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FDA Briefing Document

Cardiovascular and Renal Drug Advisory Committee Meeting

January 14, 2014

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought droxidopa to this Advisory Committee in order to gain the Committee's insights and opinions, and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

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Draft Points To Consider

1. The droxidopa resubmission comprised an additional efficacy study, study 306, which was amended to study 306B following an interim analysis where 51 patients were unblinded. The unblinded Contract Research Organization statistics team that was part of the data monitoring committee (DMC) had access to the randomization codes for all Study 306 patients and the access was not revoked until March 2, 2012; however, the sponsor states that "project-specific procedures were in place at the time to protect the blinding of the study within PPD. In addition, members of the biostatistics DMC support team were no members of the blinded project team."

    a) In general, when unblinded interim analyses occur, leading to changes in endpoints and sample size, how can the Agency gain assurance in the integrity of the amended study?

2. If study 306B were considered to be a "stand alone" study to support effectiveness:

    a) Of 89 patients randomized to droxidopa, 20 patients were excluded from the primary efficacy analysis; of 85 patients randomized to placebo, 7 patients were excluded from the primary efficacy analysis. Please comment on the missing data and effects on study interpretability.

    b) Does the baseline imbalance in fludocortisone use affect the interpretability of study 306?

    c) Is the treatment effect for a symptom benefit robust enough to constitute adequate evidence of effectiveness for a single study?

3. Evidence from two longer-term studies, 303 and 306, suggest no durability to any statistically significant endpoint. Should the symptomatic treatment of neurogenic orthostatic hypotension, a chronic condition, show evidence of durability? If not, should the sponsor conduct studies to characterize duration of effect and instructions for use (including time when resumption will be effective)?

    a) If so, should this evidence be required prior to approval or post-approval?

4. According to the Code of Federal Regulations, "FDA may grant marketing approval for a new drug product on the basis of adequate and well-controlled clinical trials establishing that the drug product has an effect on a surrogate endpoint that is reasonably likely, based on epidemiologic, therapeutic, pathophysiologic, or other evidence, to predict clinical benefit or on the basis of

an effect on a clinical endpoint other than survival or irreversible morbidity. Approval under this section will be subject to the requirement that the applicant study the drug further, to verify and describe its clinical benefit, where there is uncertainty as to the relation of the surrogate endpoint to clinical benefit, or of the observed clinical benefit to ultimate outcome." (21CFR314, subpart H, section 314.50).

Should droxidopa be considered for approval under subpart H? If yes, based on what surrogate clinical endpoint? How should clinical benefit be verified?

5. Should droxidopa be approved for the treatment of symptomatic neurogenic orthostatic hypotension? If yes, should the treatment be limited to a population with Parkinson's Disease or include patients with MSA, PAF, DBHD, and NDAD (can expand on acronyms)?

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	203202
Priority or Standard	Priority
Submit Date(s)	September 23, 2011
Received Date(s)	September 28, 2011
PDUFA Goal Date	March 28, 2012
Division / Office	Division of Cardiovascular and Renal Products
Reviewer Name(s)	Melanie J. Blank, MD
Review Completion Date	January 27, 2012
Established Name	L-DOPS (droxidopa)
(Proposed) Trade Name	Northera
Therapeutic Class	Sympathomimetic
Applicant	Chelsea Therapeutics, Inc.
Formulation(s)	Capsules
Dosing Regimen	100mg – 600 mg TID
Indication(s)	Treatment of Symptomatic Neurogenic Orthostatic Hypotension (NOH)
Intended Population(s)	Patients with primary autonomic failure (Parkinson's Disease, multiple system atrophy, pure autonomic failure, dopamine-β-hydroxylase deficiency, and nondiabetic autonomic neuropathy)

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Executive Summary and Recommendation on Regulatory Action

The applicant is seeking approval of Droxidopa for "the treatment of symptomatic neurogenic orthostatic hypotension (NOH) in patients with primary autonomic failure (Parkinson's Disease (PD), Multiple System Atrophy (MSA) and Pure Autonomic Failure (PAF)), Dopamine Beta hydroxylase (DβH) Deficiency and Non-Diabetic Autonomic Neuropathy (NDAN)." In Japan, the drug has been approved for the same indication since 1989, but is marketed at lower doses (100 – 300 mg tid) compared to 100 – 600 mg tid in this development program. In Japan, droxidopa is also approved for "freezing" associated with Parkinson's disease and for hemodialysis patients, indications that are not being sought in this development program.

Droxidopa, a prodrug, is converted mostly peripherally, but also centrally (as it passes through the blood brain barrier) into norepinephrine (NE). It is thought that patients with neurogenic orthostatic hypotension lack the ability to autoregulate their blood pressure via appropriate vasoconstriction when they rise from a supine to a standing position. Therefore, it has been thought that vasoconstrictors should convey therapeutic benefit to patients with NOH. Midodrine, the only approved drug for symptomatic neurogenic orthostatic hypotension, is a vasoconstrictor. It was given accelerated approval based on a surrogate endpoint, standing systolic blood pressure, which was thought at the time to be reasonably predictive of a therapeutic benefit. Many years have passed since initial approval (1996) and no studies have convincingly shown that there is symptom relief associated with midodrine use. Other vasoconstrictors, such as ephedrine, have not been able to show symptomatic benefit in patients with NOH. In addition to traditional methods of treatment such as getting up slowly, raising the head of the bed at night, keeping volume expanded by increasing salt and fluid intake, and fludrocortisone as a volume expander (off-label use), there are some other medications that are used off-label by patients who suffer from these conditions. Most of these drugs carry serious safety concerns. At this time, patients with symptomatic neurogenic orthostatic hypotension have few therapeutic alternatives.

Salient factors in the regulatory history of droxidopa are that 1) FDA agreed upon orphan drug designation for droxidopa and 2) there is an SPA for Study 301 whereupon it was agreed that a highly significant outcome ($P<0.00125$) in this one trial "might be sufficient" for approval. Other correspondence reflected the importance of assessing the durability of droxidopa's effect as well as the methods the sponsors used for validating the Patient Reported Outcomes measures that were used as efficacy endpoints. At the pre-NDA meeting, FDA clearly communicated the need to understand the rationale for the sponsor's claim of clinical benefit associated with the small effect

size (0.9 points) demonstrated in Study 301 on the primary endpoint [composite Orthostatic Hypotension Questionnaire (OHQ)].

From a historical perspective, it is important to note that Study 302, an enriched study that enrolled 101 patients in the double-blind phase, was the first pivotal study to be completed. It began with a titration phase wherein patients were selected to participate in the randomized part of the study only if they were responders [determined by improvement of at least one point on a symptom question (Orthostatic Hypotension Symptom Assessment (OHSA) Item 1) and an improvement in SBP of at least 10 mmHg at 3 minutes post-standing]. The droxidopa dose was forced up to the maximum dose of 600 mg tid during the titration phase as long as the systolic BP did not exceed 180 mmHg. Subsequently, the patients all stayed at their maximum titrated dose for one week. Then, there was a randomized withdrawal period of two weeks wherein the patients were randomized to either droxidopa or placebo. Despite its enrichment design, Study 302 failed on its primary efficacy endpoint - the OHSA Item 1 which was the same criterion that was used to enrich the trial. The difference between the droxidopa arms and the placebo arm was 0.6 on the OHSA Item 1, favoring droxidopa, but this difference was not statistically significant. Not only did Study 302 fail on this primary endpoint, but it failed to demonstrate an effect on standing systolic blood pressure. An exploratory analysis showed a nominally statistically significant improvement in OHQ. As a result of this finding, the sponsor proposed to change the primary efficacy endpoint of Study 301 which was practically finished at the time, to OHQ. FDA agreed.

Study 301 was initiated and enrolled 162 subjects in its double-blind phase. Also employing the same enrichment strategy as Study 302, only responders to droxidopa (determined also by improvement of at least one point the OHSA Item 1 during a 1-2 week open-label droxidopa titration phase and an improvement in SBP of at least 10 mmHg at 3 minutes post-standing) were randomized. Following the titration phase, patients that were selected by their ability to respond underwent a wash-out week, followed by double-blind randomization to placebo or the previous titrated dose of droxidopa. The results on both OHSA Item 1 and OHQ were highly statistically significant [$p < 0.001$ for OHSA Item 1 (effect size 1.3) and $p = 0.003$ for OHQ (effect size 0.9]. Also, a placebo-subtracted increase in standing systolic blood pressure (SBP) of 7.3 mmHg was demonstrated, ($p <0.001$).

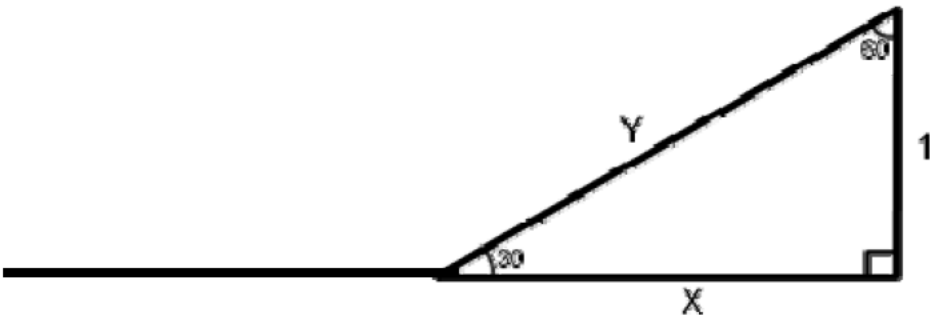
A third 102-patient study (Study 303), similar to Study 302, had a randomized withdrawal design and was an extension study of 3 1/2 months duration, enrolling mostly patients from Study 302. The patients were on droxidopa for three months during this study at their titrated dose. After three months patients were randomized to continue on their titrated dose of droxidopa or to begin placebo treatment. Study 303 was not powered to show an effect on OHQ and it did not show an effect on either OHQ or OHSA Item 1. There was a numerical difference between the droxidopa arms and the placebo arm of 0.4 on the OHSA Item 1, favoring droxidopa. This difference in OHSA Item 1 score was less than a third of what was seen in Study 301. There was also no effect on standing SBP. In fact, there was a seemingly paradoxical effect on systolic

blood pressure. The placebo arm showed no change in standing SBP whereas the droxidopa arm actually demonstrated a decrease in standing SBP of 8.4 mmHg (p = 0.29).

The safety data base of this development program was not robust. The total patient exposure in the Chelsea program was 535 patients with 276 patients exposed ≥ 6 weeks and only 64 of those were exposed to the maximum dose of 600 mg tid. A total of only 93 patients were exposed over 1 year and only 26 of those were exposed at the maximum dose of 600 mg tid. There was limited phase 3 double-blind exposure; only 131 patients received droxidopa with a mean exposure of 11 days during the double-blind phase 3 studies. This paucity of long-term exposure combined with low patient exposure at the highest dose makes it difficult to evaluate properly the long-term safety of droxidopa.

It needs to be noted that droxidopa has been designated as having an orphan indication where exposure is not expected to meet ICH E1 recommendations (1500 patients, ≥300 patients exposed for > 6 months, ≥100 for > 1 year).

Hypertension was a safety issue that had to be monitored carefully during the titration phase as some patients had hypertensive responses and required down titration or discontinuation of drug. One concern was that “supine” BP was never measured when patients were truly supine. The patients had “supine” BP measured when their heads were tilted up by 30 degrees, which is a considerable degree of tilt as shown in the diagram below. It is quite possible that the patients’ blood pressures would have been much higher if they had been lying flat.



There were 2 deaths during the short pivotal trials. One patient died prior to receiving drug or placebo. Another patient died 10 days after being discontinued from droxidopa. She had received 3 days of droxidopa and developed hypertension. She was taken off drug and then was started on midodrine. The patient died suddenly 10 days after discontinuation of droxidopa.

During the longer term open-label experience with droxidopa, there were several deaths, SAEs, discontinuations for AEs, and events of hypertensive crisis, strokes, and

myocardial infarction. There were also several patients with worsening of their movement disorders. Of utmost concern are reports of neuroleptic malignant syndrome from Japan that aren't clearly explained. In a review of Japanese postmarketing reports, there were 28 cases of neuroleptic malignant syndrome reported while patients were taking droxidopa.

Of note, these events are difficult to interpret because they were largely reported in uncontrolled extension studies, or spontaneously reported from the post-marketing period in Japan.

The decision whether or not to approve droxidopa is complex. Arguments in favor are the following:

1. There is strong evidence from one randomized controlled clinical trial (Study 301) that droxidopa confers at least one week of symptomatic benefit according to a questionnaire that pertains to the core symptoms of the disorder of symptomatic NOH, the Orthostatic Hypotension Symptom Assessment (OHSA) Item 1 with a robust p value of < 0.001. The mean effect size on this instrument was 1.3 points on a scale of 0-10 where the average baseline reading was between 5 and 6.

   While the clinical benefit associated with the effect size of 1.3 may not be well understood, this is an average response. Some patients experienced a much greater benefit. An argument can be made that droxidopa is a titratable drug and patients will be able to tell whether it is helping them and whether it is worth assuming certain safety risks.

   There is post-hoc evidence from the cumulative distribution bin analysis of study 301 on the Orthostatic Hypotension Questionnaire (OHQ) endpoint that a small segment of the population was benefitted greatly by droxidopa. See Figure 11 on p. 49. Approximately 18% patients on droxidopa compared to approximately 2% of patients on placebo improved by 4 points or better on the OHQ. This effect is larger than what would be expected in an unselected population because of the enrichment design of the trial which selected out only 60% of the patients to be randomized. If one assumes that the patient population originally enrolled in 301 is reflective of patients who would be taking droxidopa in real life experience, ~10% of patients would be expected to have such marked improvement in symptoms (18% X 60%).

   According to the 1998 FDA guidance titled, "Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products." a single trial is acceptable under certain circumstances. While arguments can be made

against considering a single trial as sufficient for approval under the current circumstances, (see arguments against approval, number 1), Study 301 has a few attributes that might give it credibility to stand alone as the sole reason to approve droxidopa:

- Large multicenter study where no single study site provided an unusually large fraction of the patients and no single investigator or site was disproportionately responsible for the favorable effect seen (Given the limited numbers of patients with this condition, this study would have to be considered "large," and the other factors are true)
- Consistency across study subjects (This was not entirely true: half of the subjects were female, 40% had PD, and 40% were >= 65, and the treatment effect was not statistically significant in these subgroups, but on the other hand, one cannot expect all subgroups to show improvements because of sample size)
- Multiple studies in a single study (Not the case here)
- Multiple endpoints involving different events (Yes, if you include the change in systolic blood pressure)
- Statistically very persuasive finding (Yes with $p < 0.001$ on the OHSA Item 1)

2. There is strong evidence from this same study that droxidopa raises standing systolic blood pressure for at least one week. There is also a relationship between systolic blood pressure increase and OHSA Item 1 improvement, albeit a weak one (exploratory analysis by Dr. Zhang shown in Figure 20).

3. There is strong evidence from one randomized controlled clinical trial (Study 301) that droxidopa confers at least one week of symptomatic benefit according to a comprehensive questionnaire [Orthostatic Hypotension Questionnaire (OHQ)] that is designed to assess symptoms that are common in patients with symptomatic orthostatic hypotension as well as the impact of those symptoms on ability to function (p value of < 0.003). The mean effect size on this instrument was 0.9 points on a scale of 0-10 where the average baseline reading was between 5 and 6.

4. Despite failing to show benefit on its primary efficacy endpoint, there was supportive evidence from Study 302 for benefit on the OHQ with a nominally significant benefit for this endpoint (effect size was 0.96, $p = 0.042$).

5. Most of the individual scores on the questions in OHQ in Study 301 showed a statistically significant benefit.

Arguments against approval follow:

1. In the FDA guidance titled, "Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products," it is clearly presented that additional proof of effectiveness is not necessary for approval when one of the following three factors is present:

   a. An effect on mortality, irreversible morbidity or prevention of a disease with a potentially serious outcome is demonstrated in one adequate and well controlled trial, AND/ OR, if conduction of another trial is not practically or ethically possible
   b. Efficacy has already been established and effectiveness in a new population or with a new formulation or for a new use can be extrapolated from existing data
   c. Demonstration of effectiveness by a single study of a drug with independent substantiation from related study data.

   It seems clear that NOH is a disease with important morbidity and mortality; however, none of the studies were designed to show effects on mortality, irreversible morbidity, or prevention of a disease with a potentially serious outcome. Certainly a 0.9-point improvement in the OHQ is not in this league.

   Strictly speaking, Study 302 was a hypothesis generating study and therefore should not be considered in the same light as a second successful study conducted with a prespecified primary endpoint. Therefore, in the droxidopa development program, there was really only one successful clinical trial, Study 301. In fact, the third study, Study 303 was unsuccessful on the OHQ primary endpoint and several other endpoints of interest and therefore, refutes several of the Study 301 findings [improvement on the OHQ, the Orthostatic Hypotension Symptom Assessment (OHSA) Item 1 and increased standing systolic blood pressure].

   If one were to strictly follow the FDA guidance paraphrased above, it is clear that there would need to be independent substantiation from related study data. The only data to consider for this purpose were the systolic blood pressure data. These data, however, did not provide evidence of consistency of effect. In fact, there was no difference between placebo and droxidopa treatment groups in either Study 302 or 303 in standing BP. If droxidopa affects the symptoms of NOH one would like to be fairly sure that the operative mechanism of action of the improvement in symptoms is

an effect on the underlying condition, namely the orthostatic change in systolic blood pressure or the standing systolic blood pressure.

While the OHQ and OHSA Item 1 effects corresponded to a statistically significant difference in standing systolic BP in Study 301, the OHQ finding in 302 did not correspond to a statistically significant standing systolic BP effect. There was a slight inverse correlation between OHQ score and systolic BP but there was a high degree of variation decreasing any confidence one might have in that relationship. In Study 303, the standing systolic BP in the droxidopa treatment group was numerically lower than in the placebo treatment group. Taking these BP data together, it appears to be clear that there is insufficient independent substantiation of effectiveness. Thus, it becomes difficult to feel comfortable approving droxidopa based on only one trial. Furthermore, the paradoxical relationships seen in Studies 302 (improvement in OHQ, no improvement in systolic BP) and 303 (relative decrease in systolic BP in droxidopa arm) might suggest that either 1) change in the OHQ may overestimate symptom benefit or 2) the symptom benefit derived from droxidopa is not related to treatment of the underlying condition but rather to a stimulant or some other type of effect.

2. The primary endpoint that was selected for Study 301, the OHQ, was reviewed by the Study Endpoints and Labeling Development (SEALD) team reviewer, Dr. Elektra Papadopoulos, and found to be lacking in content validity. The OHQ questions should have been crafted to measure the symptomatic impact when performing certain functions and/or the functional impact on the symptoms of orthostatic hypotension. It should have included questions that specifically addressed symptoms associated with postural changes and patient's ability to make those postural changes during their daily activities. Instead, it just queried the patients regarding their symptoms or their ability to stand and/or walk without drawing any relationships between these two integral concerns.

   Furthermore, the post-hoc OHQ "success" in Study 302 was driven by the benefit on standing which was asked in 2 of 10 OHQ questions (standing briefly; standing for prolonged periods – one is a subset of the other). This was the only question that showed nominally statistically significant improvement in the OHQ of Study 302. "Standing" is not a symptom and therefore cannot be used to support a symptomatic claim. It is also not clear what "standing" means. Does it mean standing up from a seated position or staying standing once you have achieved standing? And how can this positive finding be interpreted as a clinical benefit when the dizziness item (OHSA Item 1) did not show improvement? One might conclude that the post-hoc success of "standing" without improvement on

"dizziness" in Study 302 provides additional evidence that the OHQ is not a valid instrument for measuring clinical benefit.

Study 302 should not be considered to be supportive of approval, not only because 1) it was a hypothesis generating study and 2) it did not show a statistically significant improvement in systolic blood pressure, but also 3) the lack of validity of OHQ as a measure of symptomatic benefit.

3. Shire, the sponsor of midodrine, an approved drug for symptomatic orthostatic hypotension (approved under Subpart H in 1996), is currently being tasked with completing 2 adequate and well controlled trials to demonstrate midodrine's symptomatic benefit. The drug was approved based on a surrogate endpoint of systolic blood pressure because it was felt to be reasonably likely that this endpoint predicted symptomatic benefit. After several failed trials, this has not yet panned out. It is important to note that we do have strong evidence of a pharmacodynamic effect for midodrine (the increase in BP) and yet we are still demanding that they provide us with 2 trials that successfully demonstrate a clinical benefit. We should not apply lesser standards for the approval of droxidopa than we expect for midodrine.

4. There has been no durable effect (i.e., more than 1 week) demonstrated for droxidopa. Studies 302 and 303, while showing the slightest of favorable trends on OHSA Item 1 (0.6 effect size, p=0.51 for Study 302 and 0.4 effect size, p = 0.25 for Study 303), did not demonstrate clinical/ symptomatic benefit for droxidopa after two weeks and 3 months, respectively, of chronic use followed by a 2-week randomized withdrawal period. These studies also failed to show any durable effect on systolic blood pressure. The sponsors suggest that there might be a carry-over effect of droxidopa that might obscure benefit in a 2 week randomized withdrawal experience. While this is possible, an alternative explanation could be loss of effect after several weeks of treatment. It is also possible that other study-related effects such as optimization of other aspects of their treatment regimen, including optimization of other medications, increased salt and water intake, increased exercise and elevated head at bed at night may have obscured any additional benefit that droxidopa might have conferred.

   Study 306 was not submitted as part of the NDA and was not considered in this review. However, I am going to discuss it here briefly because it provides additional evidence that there is either no effect of droxidopa on the OHQ or that the effect is not durable. Study 306 was an 8-week study in Parkinson's disease patients who have symptomatic neurogenic orthostatic hypotension. The study was preceded by a two-week period wherein patients were titrated to effect on the OHSA Item 1, similarly to

studies 301 and 302. Another enrichment study, only responders were included in the induction design double-blind study period that followed. Study 306 was nearly stopped for futility upon recommendation of the data monitoring committee. Instead, an exploratory analysis convinced the sponsor to continue the study with a different primary endpoint (falls). We do not have the final study report for Study 306 and it is unknown if the trial has been completed. Without analyzing the study it is not possible to understand the reasons for failure of the interim analysis. Nevertheless, failure of Study 306 on its original primary endpoint (OHQ) in Parkinson's disease patients is not encouraging.

5. There were no pure placebo-controlled data making a proper safety assessment unfeasible. All patients had been exposed to droxidopa prior to being randomized to placebo. Therefore, none of the events that occurred while patients were on placebo could be confidently assigned as "background events." Generally, adverse events that occur well after discontinuation of a drug (>> 5 half-lives) are not attributed to the drug. But if the applicant is correct about carryover effects on efficacy after patients discontinue droxidopa and switch to placebo, such carryover effects would apply to droxidopa's safety profile as well, obfuscating the controlled safety data from studies 301, 302, and 303. Furthermore, the "supine BP" was measured with head-up tilt of 30 degrees. For this reason, true supine hypertension was not assessed. This is a great deficiency because supine hypertension may have been grossly underestimated in this development program as a result of this design factor.

6. There were numerous concerning safety findings: 2 deaths in the double-blind phase, 17 deaths, 1 stroke on post-mortem examination and 1 other stroke in a patient who survived, 3 AEs of hypertensive crisis, 1 myocardial infarction (resulted in death), 1 case of coronary artery disease that resulted in discontinuation, 33 cases of worsening of underlying movement disorder including 2 SAEs in addition to many other SAEs and discontinuations. Droxidopa is converted into NE which is a vasoactive substance. It is plausible that the cardiovascular adverse events were related to vasoconstriction from NE. Additionally, in the Japanese postmarketing experience, there were 28 reported cases of neuroleptic malignant syndrome, an often fatal condition. A few of these cases appeared to have no likely etiology other than droxidopa for what is considered to be a serious iatrogenic condition. The data that the sponsor provided were insufficient to conclude or exclude causal relationships. It is difficult and imprudent to assign causality to droxidopa because of the mostly open-label design of the study and the nature of postmarketing reporting periods. Nevertheless, the specter of serious safety issues related to droxidopa has been raised and should not be ignored.

7. Risk: Benefit analysis: The effect size of 1.3 in the OHSA Item 1 is not easy to interpret. The sponsor provided an anchor-based method of analysis wherein they attempted to equate changes in a general symptom measure tool (Clinical Global Impressions-Severity) to the OHQ and to the OHSA Item 1. The analysis was difficult to interpret and one could not feel confident in the end that a 1.3 change truly had clinical significance. Without understanding the magnitude of benefit from droxidopa, it is hard to weigh safety concerns against efficacy for the purposes of approval and labeling. This is particularly concerning in this setting where the safety database is relatively small and difficult to analyze.

In summary, in support of approval, there is one trial (Study 301) that is strongly supportive of efficacy of droxidopa and contains many of the attributes of a single trial that might stand alone to support efficacy: large and multicenter trial, improvement on multiple ordered endpoints including OHSA Item 1, OHQ and systolic blood pressure, and statistically very persuasive findings. From a post-hoc analysis of the cumulative distribution bin analysis of Study 301, there was a much larger group of patients that had a greater level of improvement (improvement of ≥4 points on the OHQ) on droxidopa than on placebo. Study 302, the OHQ hypothesis generating study for Study 301, might be considered supportive of efficacy if one considered OHQ to be a valid endpoint.

Against approval, there is effectiveness of droxidopa in one trial only. Furthermore, the strength of evidence of efficacy does not meet the standards set forth in the FDA guidance titled, “Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products” because 1) there is no improvement demonstrated on mortality or irreversible morbidity, 2) there is no ethical or practical reason to not conduct another trial, 3) there was no evidence of pharmacological effect in the randomized withdrawal trials: either “supportive” Study 302 or Study 303 and 4), there is no other compelling evidence of efficacy from the clinical trials that was submitted for Agency review. There is even evidence against the efficacy of the drug that came from other studies: 302 (failure to demonstrate improvement in OHSA Item 1 despite being enriched for this effect and failure to demonstrate improvement in BP), 303 (failure to demonstrate improvement in OHSA Item 1 or OHQ and paradoxical lowering of systolic BP) and 306 (failure to demonstrate improvement on OHQ, also despite enrichment). Study 302 should not be considered supportive of efficacy for two additional reasons: 1) it was a hypothesis generating study because its post-hoc success on the OHQ came before study 301; and 2) The OHQ, is difficult to interpret and there is great discomfort with considering it to be a valid symptom endpoint measure.

An important consideration is that the standards that we are setting for the approval of midodrine are higher than one successful trial despite midodrine's demonstration of a pharmacological effect. Another argument against approval is that there is no evidence of durability of effect. Study 301 only demonstrated effectiveness for 1 week. That is not sufficient for a drug that is intended to treat a chronic condition. Also against approval is that there was no pure placebo-controlled safety data and there were safety signals that were concerning including deaths, strokes, myocardial infarction, progression of underlying disease and hypertensive crisis. Supine hypertension may have been underestimated because of the way it was measured with head-up tilt of the bed to 30 degrees. Droxidopa gets converted into NE which is a vasoconstrictor. From a theoretical standpoint, vasoconstriction is likely to exacerbate cardiovascular disease and it is quite plausible that the cardiovascular events that were seen in the development program were caused by droxidopa. Arriving at a risk-benefit assessment is extremely difficult when the possible effect size of the drug (1.3 on the OHSA item 1) is hard to understand and the safety of the drug is poorly understood but could be ominous.

The primary reason to not recommend approval is the lack of sufficient evidence of efficacy. There is only one successful trial and it is well known that random factors can cause erroneous clinical trial outcomes. Patients with symptomatic neurogenic orthostatic hypotension are vulnerable and it is important to ensure their safety by protecting them from exposure to drugs that may not be effective, particularly drugs that have a theoretical basis for causing cardiovascular safety issues, as this drug has. Additionally, the lack of evidence of durability is particularly concerning. Patients should not be exposed to a drug chronically unless benefit is established over a reasonable amount of time – at least three months. It is possible that there is a down regulation of NE receptors in the peripheral circulation after prolonged exposure to droxidopa. If this is the case, one might consider approval but would need to label the product differently than what is being currently proposed (long-term use). Durability of effect should be studied further so that proper instructions for use can be crafted. Finally, the safety of droxidopa is still poorly characterized and another properly designed trial should be conducted to evaluate it. This development program was not properly designed to evaluate safety because of three factors: 1) the absence of a pure placebo group, 2) most of the safety data were collected in open-label trials and 3) blood pressure was collected with the head of the bed tilted at 30 degrees. Vasoconstriction is the mechanism of action of droxidopa. Therefore, without a control group, it is logical to assume that the cardiovascular adverse events, and there were many, were caused by droxidopa. There is also the concern of neuroleptic malignant syndrome. Since there were some Japanese postmarketing cases that were not explicable on the basis of other drugs known to cause the syndrome, one needs to be concerned that droxidopa may cause this sometimes fatal condition.

2 Introduction and Regulatory Background

2.1 Product Information

Droxidopa is a synthetic amino acid analog that is directly converted or metabolized to NE in a single step by DOPA-decarboxylase. The conversion of droxidopa to NE can occur peripherally and/or centrally. In addition to its function as an NE precursor, droxidopa promoted the release of NE from the nerve endings in experiments using brain synaptosomes and slices.[1]

2.2 Tables of Currently Available Treatments for Proposed Indications

The proposed indication for droxidopa is for symptomatic neurogenic orthostatic hypotension (NOH) in patients with primary autonomic failure (Parkinson's Disease (PD), Multiple System Atrophy (MSA) and Pure Autonomic Failure (PAF)), Dopamine Beta Hydroxylase (DβH) Deficiency and Non-Diabetic Autonomic Neuropathy (NDAN).

There is only one approved drug (midodrine) for this condition that may soon be removed from the market because it has never been demonstrated to have clinical effectiveness (improve symptoms). Midodrine received subpart H accelerated approval in 1996 for its effects on raising systolic blood pressure (SBP) which was considered at the time to be a surrogate marker of effectiveness for symptomatic neurogenic orthostatic hypotension because it was considered reasonably likely to predict clinical benefit.

The conditions for which the sponsor, Chelsea Therapeutics, Inc., is proposing to have droxidopa indicated are considered to be rare and often disabling and are accompanied by symptoms of dizziness, weakness, syncope and falls. Patients often become confined to a wheel chair or bedridden and suffer from many comorbid conditions such as infection and fracture. There are many people who develop secondary autonomic failure from other conditions such as diabetic neuropathy, or simply from advanced age. This other group of patients increases the possibility of a wide off-label market for droxidopa.

Table 1 includes a list of all of the drugs used (for the most part, off-label) for neurogenic orthostatic hypotension.

Table 1: Table of Drugs Used for Neurogenic Orthostatic Hypotension

Compound	Contraindications	Main side effects
Desmopressin	Hyponatremia, chronic renal failure Pregnancy Category B	Hyponatremia, water intoxication, headache, nausea, rhinitis
Dihydroergotamine	Myocardial ischemia, uncontrolled hypertension, renal or hepatic failure, hemiplegia or basilar migraine, peripheral artery disease, sepsis, following vascular surgery, pregnancy, nursing mothers Not to be given with vasoconstrictors or ergot-type medications	Myocardial ischemia, stroke, ventricular tachycardia, ventricular fibrillation, vasoconstriction, paresthesias hypertension, headache
Erythropoietin	Uncontolled hypertension, known hypersensitivity Pregnancy Category C	Pure red cell aplasia, infection, congestive heart failure, thrombosis of vascular access, cardiac angina pectoris, arrhythmia and cardiac arrest, hypertension, stroke, increased risk of tumor progression
Fludrocortisone	Systemic fungal infections, known hypersensitivity Pregnancy Category C	Hypertension, edema, hypokalemia, compression fractures hypomagnesaemia, congestive heart failure, headache mental disturbances
Indomethacin	Peripoerative pain in the setting of coronary artery bypass graft, known hypersensitivity, Pregnancy Category C	Myocardial infarction, stroke, pulmonary hypertension, gastrointestinal bleeding, exfoliative dermatitis, aggravation of psychiatric and neurologic conditions including Parkinson's, renal failure
Midodrine	Severe heart disease, acute renal disease, urinary retention, pheochromocytoma, thyrotoxicosis, persistent or excessive supine hypertension Pregnancy Category C	Supine hypertension, paresthesias, pruritus, piloerection, chills, urinary urgency, frequency and retention
Octreotide (somatostatin)	Known hypersensitivity to drug Pregnancy Category B	Nausea, abdominal colic, diarrhea, cholelithiasis, bradycardia, hypthyroidism, goiter, hypertensive crisis, thrombocytopenia
Pyridostigmine	Mechanical intestinal or urinary obstruction, caution with bronchial asthma Safety in pregnancy not established	Abdominal colic and loose stools, muscle cramps, muscle weakness, rash
Yohimbine	No contraindication found in verterinary label	Dogs show apprehensiveness

Sources:
Maule S et al, Orthostatic Hypotension: Evaluation and Treatment, Cardiovascular and Haematological Disorders-Drug Targets, 2007, 7, 63-70.
Low P and Singer W, Management of Neurogenic Orthostatic Hypotension: an Update, Lancet Neurol 2008;7:451-8.

2.3 Availability of Proposed Active Ingredient in the United States

The active ingredient will need to be manufactured. It is currently not available in the United States except for experimental purposes.

2.4 Important Safety Issues with Consideration to Related Drugs

Midodrine is the only approved drug for symptomatic neurogenic orthostatic hypotension (NOH). It works similarly to droxidopa presumably by causing vasoconstriction. Supine hypertension is a concerning safety issue with midodrine and there is a boxed warning about the increased risk for supine hypertension in the midodrine label. Supine hypertension can theoretically increase the risk of acute and chronic cerebrovascular disease.

Fludrocortisone is used routinely in patients with symptomatic NOH. Because of the salt and water retention that it causes, it has limited utility in the elderly.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

In the presubmission communications, FDA agreed upon orphan drug designation in a January 17, 2007 correspondence. On May 1, 2007, in the Pre-IND meeting, FDA stated that one study with a p value of ~ 0.00125 might be adequate for approval. On February 15, 2008, FDA agreed upon a SPA for Study 301 and agreed that the length of patient exposure was adequate for the safety evaluation. The Division stated that they expected two trials with $p<0.05$ to support efficacy. In a correspondence of January 20, 2010, in response to a major amendment of Study 301, FDA agreed upon a change in primary endpoint (from OHSA Item 1 to OHQ). In the Pre-NDA meeting on December 10, 2010, the FDA reminded Chelsea that one trial is not usually sufficient for approval. FDA asked for validation data for the PRO instruments used in the studies and to provide justification for how the effect size of 0.9 on the OHQ is a clinically meaningful one.

2.6 Other Relevant Background Information

2.61 Description of Symptomatic Neurogenic Orthostatic Hypotension

Definition of NOH:
"Orthostatic hypotension (OH) is a reduction of systolic blood pressure (SBP) of at least 20 mmHg or diastolic blood pressure (DBP) of at least 10 mmHg within three minutes of standing. It is a physical sign and not a disease. An acceptable alternative to standing is the demonstration of a similar drop in blood pressure (BP) within three minutes, using a tilt table in the head-up position, at an angle of at least 60 degrees." (Consensus Statement, 1996)[1].

Orthostatic hypotension may be a severely disabling condition that can seriously interfere with the quality of life of afflicted subjects. Some patients become confined to a wheelchair and some become bedridden. There are no currently available therapeutic options that have been demonstrated to have symptomatic benefit. The limitations of currently available therapeutic options, and the incapacitating nature and often

progressive downhill course of disease, point to the need for an improved therapeutic alternative.

Symptomatic NOH results from failure of the autonomic nervous system to respond appropriately to changes in posture, resulting in orthostatic hypotension (OH) on standing, and often, hypertension when supine. When individuals with NOH move from supine to standing, blood pools in the lower extremities, leading to a drop in BP and symptoms of inadequate perfusion of the brain (dizziness, faintness, lightheadedness, blurred vision, weakness, fatigue), muscles (paracervical or lower back pain), heart (angina), and kidneys (oliguria, azotemia).[2] Symptomatic NOH can be a debilitating condition for some patients, in that every time they stand, they experience a sudden, extreme drop in BP that can result in dizziness, impaired vision, weakness, fatigue, an inability to think clearly, as well as a decreased ability to conduct activities of daily living that involve standing or walking. Patients may also lose consciousness and fall, increasing the risk of fractures and head trauma,[3] factors that contribute to morbidity, disability, or death.[4] Fear of these types of injuries can result in patients limiting their activities, which leads to a host of complications ranging from a reduction in muscle mass and overall fitness, to depression, feelings of social isolation, and loss of independence.[5,6] Furthermore, longitudinal studies have shown that chronic OH increases the risk of mortality[7,8,9] stroke[10] and myocardial ischemia / infarction.[11]

Patients have high intra-individual variability in postural BP[12,13] and lose their usual diurnal variability for blood pressure or have reversal with higher blood pressures occurring at night.

Autonomic dysfunction disorders, encompassing Pure Autonomic Failure (PAF, also called idiopathic OH or Bradbury-Eggleston syndrome), Multiple System Atrophy (MSA, formerly also referred to as Shy-Drager syndrome), Parkinson's disease (PD), Non-Diabetic Autonomic Neuropathy (NDAN), or Dopamine Beta Hydroxylase (DBH) Deficiency (an enzyme that converts dopamine to NE), differ in etiology and pathophysiology; however, each condition is accompanied by a deficiency of NE.

The diseases classified under primary autonomic failure (PAF, MSA, and PD) are all neurodegenerative and of unknown etiology.

Non-diabetic autonomic neuropathy can be caused by a number of factors, including autoimmune, environmental, and infectious agents. These conditions are associated with either degradation of peripheral NE nerve function or failure of the central mechanism controlling the release of NE. The cause of DBH Deficiency is a rare genetic mutation that results in the loss of this key enzyme in NE production, resulting in a global NE deficiency and a surplus of the NE precursor dopamine.

2.62 Droxidopa Approval in Japan

Droxidopa was approved in Japan in 1989 for the treatment of orthostatic hypotension in familial amyloid polyneuropathy and Shy-Drager Syndrome (SDS, now known as MSA, multiple system atrophy) and for the relief of frozen gait or dizziness upon standing up associated with Parkinson's disease. It was also approved in Japan in 2000 for the alleviation of vertigo, staggering, dizziness on standing up, lassitude, and weakness in hemodialytic patients with orthostatic hypotension. This product has not been marketed in the U.S. It should be noted that the clinical experience in Japan supports individualized treatment with droxidopa. It is clearly stated in the Japanese label that under no circumstances should the dose exceed 900 mg in 2 or 3 divided doses.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

There are no apparent problems with the quality and integrity of the submission.

3.2 Compliance with Good Clinical Practices

Pending review by Division of Scientific Investigations.

3.3 Financial Disclosures

There were 4 disclosures (including a (b) (6) /principal investigator):

(b) (6) .: $138,400.00 including $127,400.00 in consulting fees and $11,000.00 in honoraria. (b) (6)

(b) (6) (b) (6)

(b) (6)

(b) (6) .: $95,991.51 including a study grant of (b) (6) , consulting fees of $12,712.00 and honoraria of $22,000.00. (b) (6)

(b) (6)

(b) (6) $29,500.00 including consulting fees of $17,000.00 and honoraria of $12,500.00. (b) (6) .

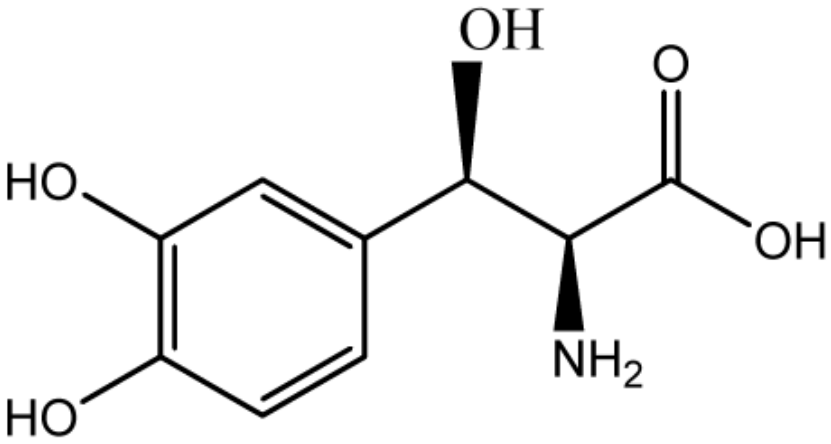
REVIEWER'S COMMENT(S): Only two of the patients from these investigators' sites were enrolled in Study 301. This does not affect the study results at all. Most of the patients of these above listed investigators were in Study 302. There were 7 subjects in the droxidopa group and 3 subjects were in the placebo group. They did show a favorable treatment difference in the OHQ, but this is not as much of a concern because of the overall failure of study 302.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The structural formula of droxidopa ((—)-threo-3-(3,4-Dihydroxyphenyl)-L-serine) is displayed in Figure 1.

Figure 1: Structural Formula of Droxidopa



Molecular weight: 213.19
Molecular formula: C9H11NO5

There were several chemistry issues during the review of this application that have now been resolved. See Dr. Lyudmila Soldatova's review.
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4.3 Preclinical Pharmacology/Toxicology

Several potential safety issues have been raised during the course of the nonclinical Pharm/Tox review process and are thoroughly discussed in the Pharmacology/ Toxicology review by Dr. D. Jensen. These are summarized below:

1. Concerns were originally posed regarding the potential neurotoxicity of a droxidopa degradant 3,4-dihydroxyphenylacetaldehyde (DOPAL). DOPAL has been reported to possess neurotoxic effects both in vitro and in vivo. Also, it has been shown to be detected in human plasma after oral administration of droxidopa, and has been shown to be markedly elevated in some Parkinson's disease patients treated with droxidopa.[14] Since droxidopa crosses the blood-brain-barrier and is likely to be converted into DOPAL in the CNS, the potential for CNS toxicity was raised. The sponsor was asked to provide additional information to help address this issue. Their response was that there is no known naturally-occurring metabolic pathway by which droxidopa, and by extension NE, can be converted into DOPAL. Further, the high levels of DOPAL reported in a couple of patients (Holmes et al, 2010) were attributed to an error with the assay methodology that resulted in inadvertent conversion of droxidopa to DOPAL. In addition, levels seen in patients treated with the widely used dopamine precursor levodopa (L-DOPA) would be expected to be much higher. Therefore, the sponsor maintained that DOPAL is not a safety concern.

   Although it appears that DOPAL is not enzymatically formed from droxidopa, another potentially neurotoxic metabolite, DOPEGAL, may be formed from NE. It is possible that droxidopa could result in increased intracerebral levels of DOPEGAL and could, therefore, result in significant neuronal loss and worsening of patients' underlying conditions. A relatively straight-forward experiment could be conducted in animals to help assess the risk to humans under therapeutic conditions. For example, rats can be given droxidopa daily (e.g., up to 28 days) using oral doses sufficiently above the human therapeutic dose, then sacrificed at various times and regions of the brains examined microscopically. Such a study should allay our concerns of whether droxidopa when given orally at some dose crosses the blood-brain-barrier in sufficient quantity to result in significant CNS toxicity or neuronal loss, regardless of the mechanism or metabolite involved.

2. Data regarding serum metabolites or their levels after repeat dosing in animals was incomplete. Additional information has been requested from the sponsor. Four human metabolites of droxidopa were evaluated by the CDER Computational Toxicology Group. Each of the four metabolites was predicted to be positive in more than one genotoxicity assay, two were predicted to be positive in 2-year rodent carcinogenicity assays, and a third has been previously shown to produce tumors in rats. It should be noted that the two rodent carcinogenicity studies were judged to be negative. One human metabolite was predicted to be teratogenic in rabbits. While the actual rabbit teratogenicity studies were negative, it is not known whether

rabbits produce that metabolite. In order to be reassured that this droxidopa metabolite is not teratogenic, it is important to know if sufficient levels are produced in the rabbit to explore this potential safety issue. An assessment of existing metabolite data from animals and humans will be important for evaluating the adequacy of the animal reproductive toxicity studies and of the rodent carcinogenicity assays for human risk assessment. However, the sponsor contends that there is a consistent metabolic pattern for droxidopa across 5 species (mice, rats, dogs, monkeys, and humans) based on available data, and that the negative carcinogenicity and teratogenicity results in animals provide an adequate assessment of human risk.

3. Studies in rats showed that interference with L-aromatic-amino-acid decarboxylase with carbidopa diminished or abolished the pressor effect produced by droxidopa. Given that carbidopa is routinely given to Parkinson's disease patients treated with L-DOPA, inhibition of peripheral L-aromatic-amino-acid decarboxylase might limit the efficacy of droxidopa in this patient population.

4. Preclinical pharmacokinetic data using lower doses of droxidopa were very limited and there were no toxicokinetic data from higher drug doses that would allow direct comparison of drug exposures during toxicology studies to clinical drug exposures. Until such data become available, it will be difficult to relate exposures seen in animals to human therapeutic exposures, although other dose extrapolations (e.g., surface area) may be used.

5. Toxicity studies in animals showed a dichotomy between species with regard to the toxicity of droxidopa. Droxidopa was essentially nontoxic at the highest doses tested in 52-week dog studies and in 13-week studies in rhesus monkeys. The highest does tested in dogs and monkeys were 30-fold greater than the highest recommended clinical dose, when based on body surface area.

   In contrast, all studies in mice and rats, including single-dose studies in each species, demonstrated renal tubular toxicity and cardiac myocyte toxicity. Also, gross renal lesions were also observed in the F1 offspring of female rats dosed with droxidopa on days 7 through 17 of gestation. Renal and cardiac lesions were observed at doses that, based on body surface area, were similar to or lower than the highest recommended clinical dose of droxidopa.

   The reasons for the marked differences in toxicity between the various species were not clear. Cardiac and renal lesions have been shown to be normal age-related degenerative disease processes in rodents, and the drug may simply exacerbate this process. It has been shown that some drugs that exacerbate spontaneous renal disease (i.e., chronic progressive nephropathy) in rats do not affect humans. Also, it has been reported that rats have a much higher density of α1-adrenergic receptors in the cardiac ventricle than do several other species and that this caused rats to

have a greater cardiac inotropic (contractile force) response following α1-adrenergic stimulation than was observed in the other animal species. This could explain the myocardial damage produced by a drug (i.e., droxidopa) that is a NE precursor. However, the occurrence of renal and cardiac lesions in young rodent animals during single-dose studies seems to argue against this premise.

Given the current uncertainty of these cardiac and renal findings in animals and their relevance for humans, it was recommended by the Nonclinical Reviewer, Dr. Jensen, that the ongoing clinical study in renal-impaired patients be completed before final approval is considered. Also, due to the myocardial necrosis and scarring observed in both rats and mice, it was recommended that the sponsor provide clinical cardiac troponin measurements, as requested previously, or even conduct noninvasive cardiac echocardiography (ECHO).

(Summarized by T. Papoian from draft Pharm/Tox review by D. Jensen - 1/24/12)

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

- Droxidopa is an orally administered, synthetic amino acid catecholamine acid pro-drug that is converted through the catecholaminergic metabolism system, specifically by L-aromatic-amino-acid decarboxylase (DOPA decarboxylase), to produce NE. While the mechanism is not well characterized, NE presumably binds to alpha adrenergic receptors in the vascular smooth muscle of arterioles causing vasoconstriction and consequent elevation of systolic blood pressure. Norepinephrine may also have an effect on venous vascular resistance. By elevating the blood pressure, it promotes the maintenance of cerebral blood flow, thereby lessening the symptoms of neurogenic orthostatic hypotension; primarily dizziness, lightheadedness and syncope.

  Droxidopa crosses the blood brain barrier and therefore may exert its effect both peripherally and centrally by increasing NE production.

4.4.2 Pharmacodynamics

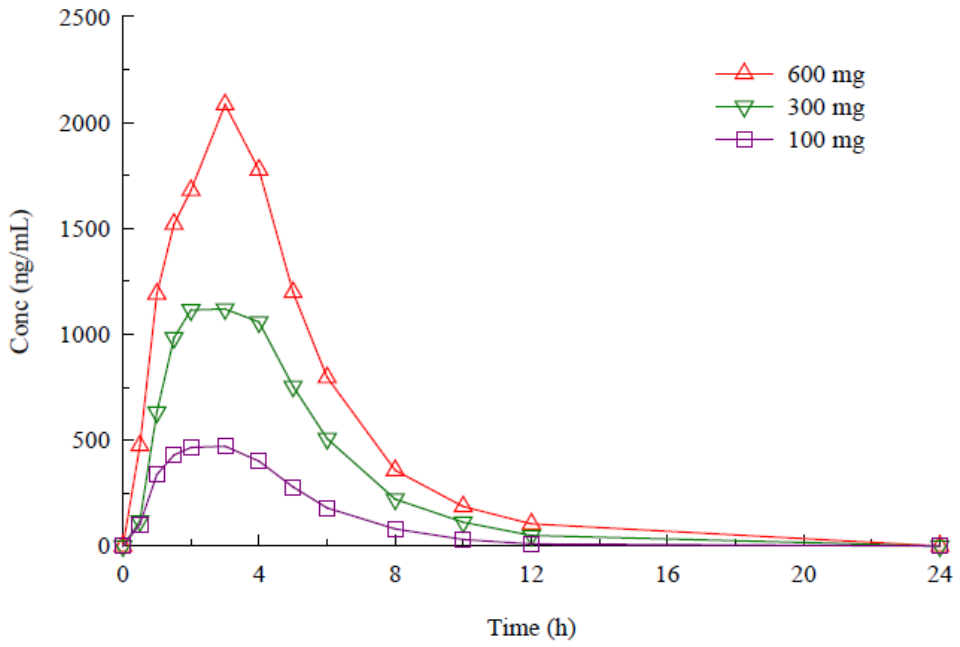
- Doxidopa's average elimination half-life is 2.5 hours. The proposed dosing regimen requires droxidopa to be administered every 4 hours during the day.
- The plasma protein binding for droxidopa is concentration dependent (decreases from 75% to 25% with increase in concentrations from 0.1 to 10 ug/mL).
- Droxidopa crosses the blood brain barrier in animals and humans.

- The major active metabolite of droxidopa is NE. Other metabolites identified in humans and animals include methylated droxidopa (3-OM-DOPS), vanillic acid (VA) and protocatechuic acid (PA). These metabolites are reported to have some vasomotor activity.
- Approximately 70% of droxidopa and its metabolites are excreted in urine in animal studies.
- Droxidopa is metabolized by non-CYP mediated pathways and involves catecholamine systems in its metabolism. *In vitro* studies indicate that droxidopa has low CYP induction or inhibition potential.
- The moderate food effect observed for droxidopa with high fat meal (34% and 20% reduction in C_{max} and AUC) are not clinically significant and the phase 3 trials were conducted without any food restrictions. Therefore, droxidopa can be administered with or without food.

4.4.3 Pharmacokinetics

The PK of droxidopa was studied in single-dose (studies 20/1859-94, 20/1860-94) and multiple-dose (study 101) designs in healthy subjects. There was a dose-related increase in exposure up to 600 mg dose as shown in Figure 2. The 900 mg tid dose overlapped with the 600 mg tid dose (not shown).

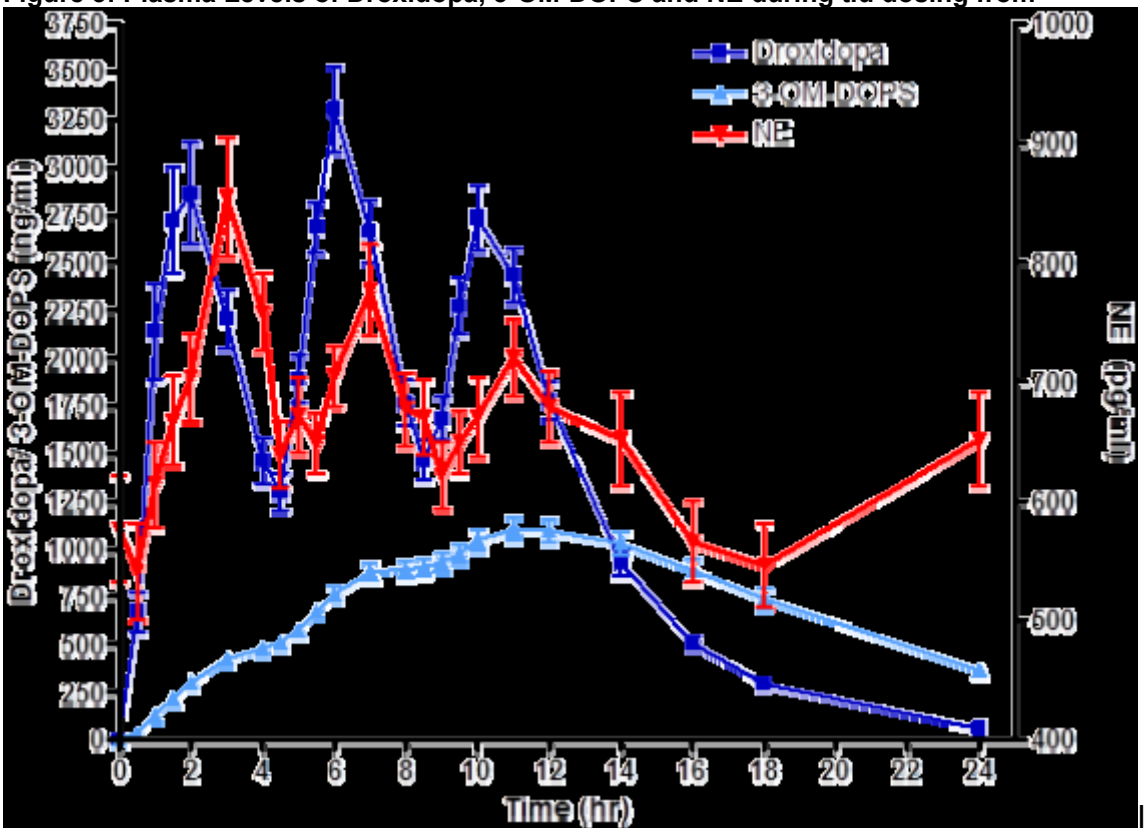
Figure 2: PK Characteristics of Droxidopa from Study 20/1860-94 (N=20)



Source: Figure 2-20, Summary of Clinical Pharmacology Studies, Section 2.7.2.2.2.3.2, p. 32.

The terminal elimination half-life of droxidopa ranged from 2.1 to 2.4 hours. The major metabolite 3-OM-DOPS also showed dose-dependent increase in exposure up to 600 mg dose level and had an elimination half-life of 4.7 to 5.3 hours. Norepinephrine levels also increased in a dose related fashion. As shown in Figure 3, NE levels peaked shortly following the droxidopa peaks as one would expect.
There was no significant accumulation of droxidopa on multiple dose administration in a TID regimen.

Figure 3: Plasma Levels of Droxidopa, 3-OM-DOPS and NE during tid dosing from

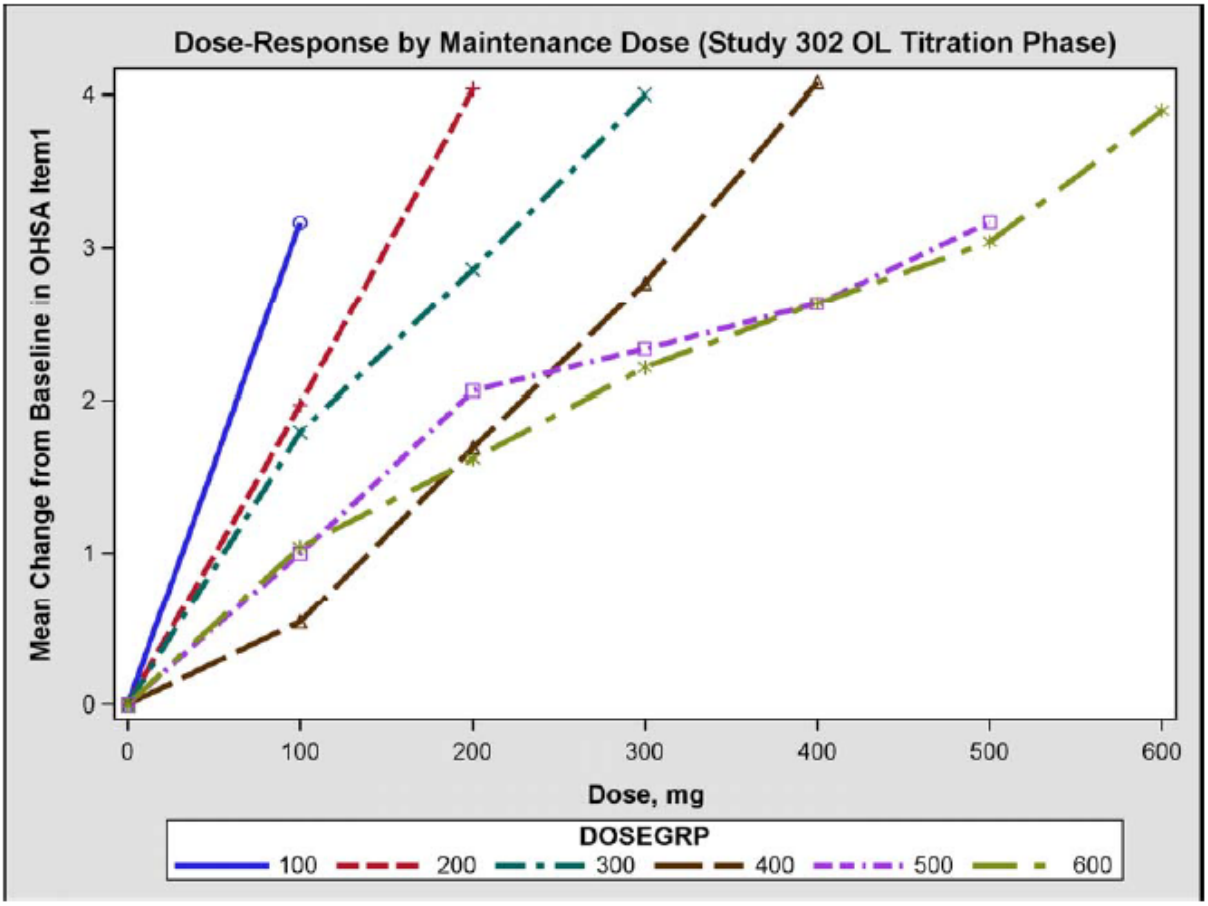


IND 110587Review by Dr. Leonard Kapcala, 12/16/10

The clinical pharmacology reviewer, Dr. Sreedharan Sabarinath, characterized the dose relationship between droxidopa and OHSA Item 1 and systolic blood pressure. As can be seen in Figure 4, as the dose of droxidopa was titrated in Study 302 in the groups of patients on 200 mg tid to 600 mg tid, the average effect on OHSA Item 1 (dizziness, lightheadedness, feeling faint or feeling like you might black out) increased – at least until 400 mg tid. 181 patients were included in the titration phase of the study. Each day patients had their doses titrated to the next higher dose unless they became asymptomatic, had a rise in the systolic blood pressure to >180 mmHg or an adverse reaction related to titration. While it is attractive to think that the OHSA Item 1 response is dose related, without placebo titration arms, one cannot be sure that this titration

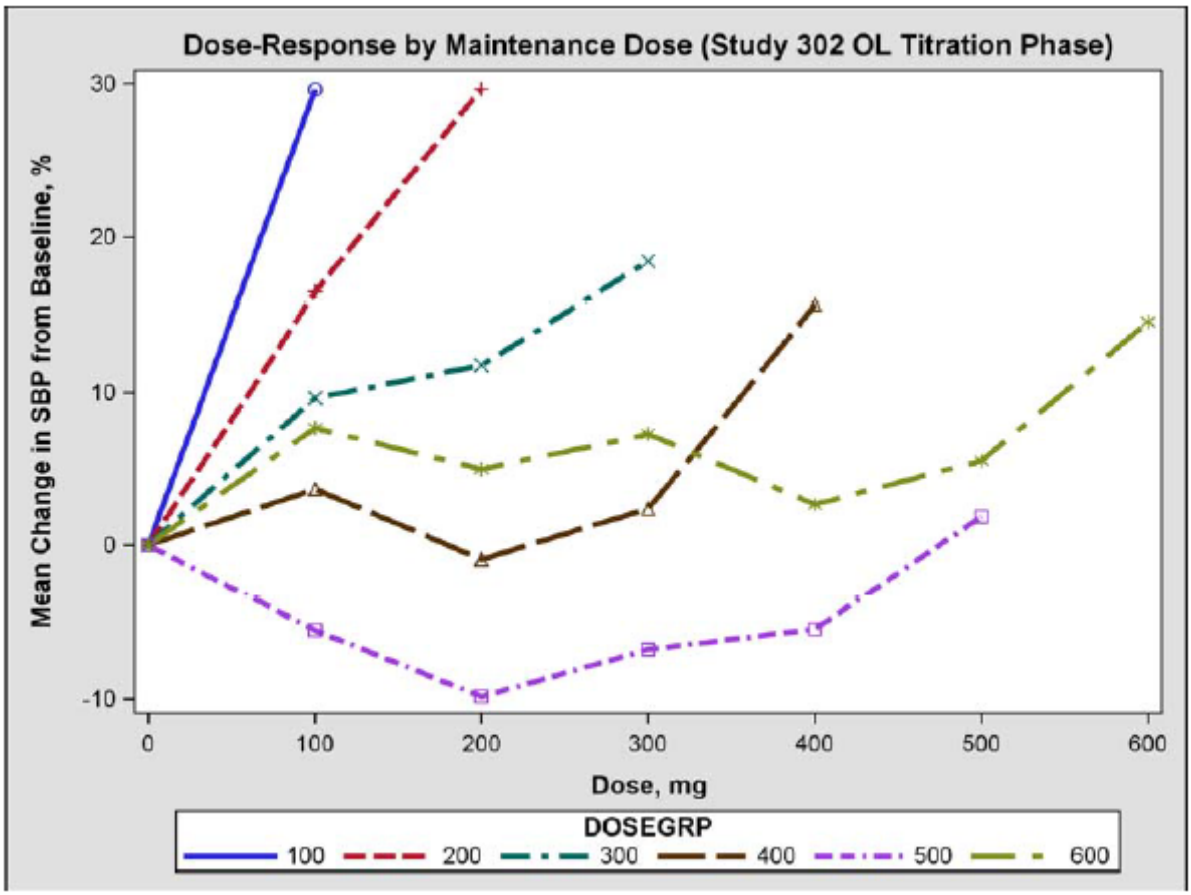
effect isn't based on some other study-related factor aside from dose (e.g., volume repletion, head-up tilt, increased time out of bed).

Figure 4. Dose-Response on OHSA Item 1 by Maintenance Dose (Study 302 Open Label)



Dr. Sabarinath did another analysis that showed that there is no dose response for droxidopa on SBP past the 300 mg dose. This is shown in Figure 5. In fact, there is only an apparent dose response for the 200 mg and 300 mg tid doses. For higher doses, it appears that droxidopa fails to have an effect on SBP. The patients on the higher doses who had no average rise in SBP also took longer to have a change in their OHSA 1. It appears from these graphs that the effect on systolic blood pressure is not necessary to elicit an effect on OHSA 1 in patients who are titrated to these higher doses. The mechanism of action of droxidopa is presumed to be an indirect effect on symptoms via a change in blood pressure. The uncoupling of the symptom score from the SBP effect makes one wonder about the true mechanism of effect of droxidopa and/or question the validity of the symptom score.

Figure 5. Dose-Response on SBP by Maintenance Dose (Study 302 Open Label)



5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

There were 6 studies in the clinical development program as shown in Figure 6. All but Study 306 will be discussed in this review. Study 306 is an ongoing study in Parkinson's disease patients and data from that study were not included in the NDA submission. FDA agreed in a presubmission meeting that Study 306 data did not need to be included in this NDA.

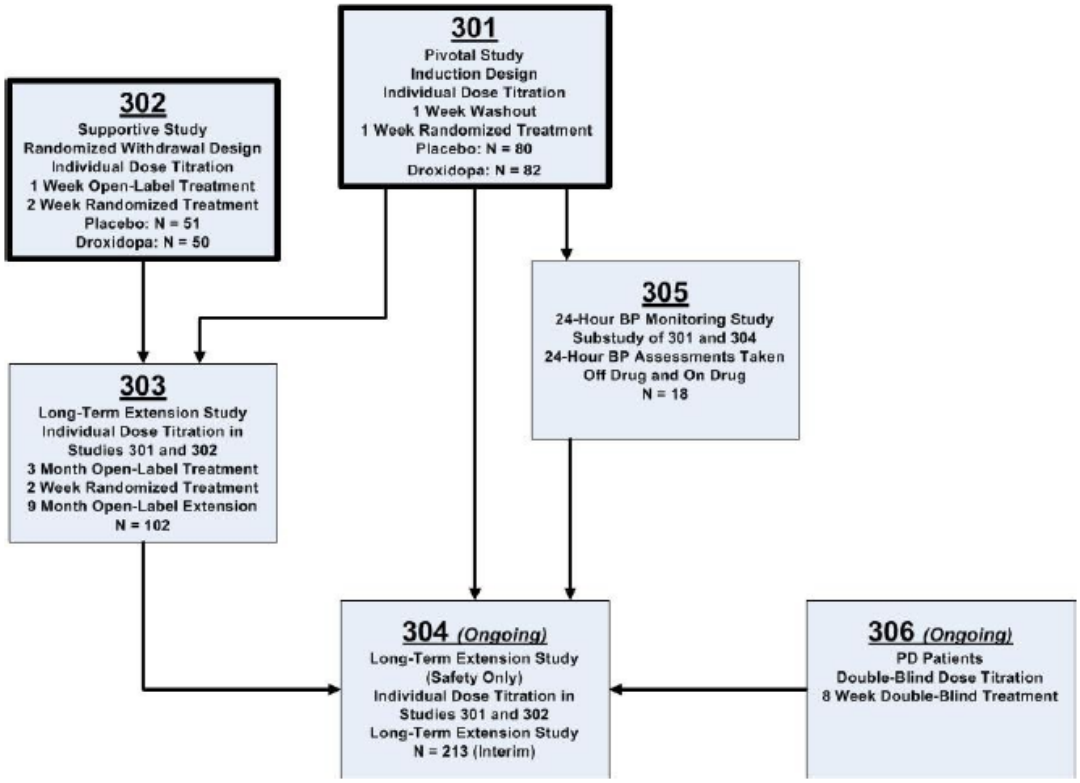


Figure 6. Clinical trials

5.2 Review Strategy

To conduct my review I read the regulatory history, the sponsor's documents including study reports and integrated reports, familiarized myself with the literature on the topic of neurogenic orthostatic hypotension, and conducted my own analyses using the datasets that were provided by the sponsor. I also reviewed IND safety reports that have been submitted since the NDA was submitted.

5.3 Discussion of Individual Studies/Clinical Trials

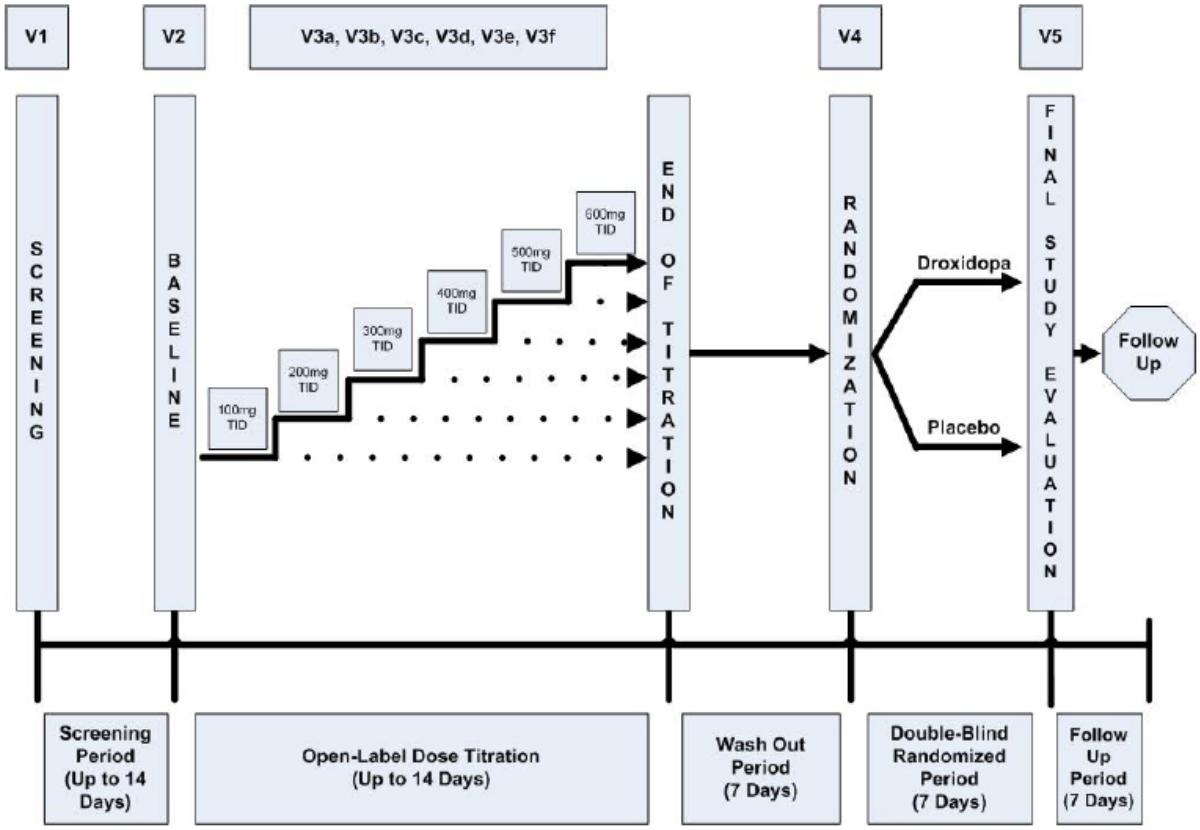
5.3.1 Study 301

Title: A Multi-Center, Double-Blind, Randomized, Placebo-Controlled, Parallel-Group, Induction-Design Study to Assess the Clinical Effect of Droxidopa in Subjects with Primary Autonomic Failure, Dopamine Beta Hydroxylase Deficiency or Non-Diabetic Neuropathy and Symptomatic Neurogenic Orthostatic Hypotension
Study Centers: 94 centers in 9 countries

Study Period:
Study Initiation Date: August 22, 2008 (first patient enrolled)
Last patient before amendment completion date: September 28, 2009
Primary Efficacy Endpoint Change (protocol amendment 4): December 11, 2009
First patient completed after amendment: March 5, 2010
Study Completion Date: July 23, 2010

Methodology/ Study Design: Study 301 (Figure 7) was a phase 3, multi-center, multi-national, double-blind, randomized, placebo-controlled, parallel-group, induction-design study with an initial open-label dose-titration, followed by a 7-day washout period, followed by a 7-day double-blind randomized treatment period with at least 75 patients randomized to placebo and at least 75 patients randomized to droxidopa. The study was designed to evaluate the clinical effect (efficacy and safety) of droxidopa treatment (versus placebo) in patients with symptomatic NOH and PD, MSA, PAF, DBH Deficiency, or NDAN.

Figure 7: Study Design for Study 301



TID=Three times daily.

Source: Figure 9-1, Study Report for Study 301, section 9-1, p. 20.

The study consisted of an initial Screening Period (up to 14 days) to confirm eligibility, an open label titration phase (up to 14 days), followed by a 7 day washout period and a 7 day double-blind randomized treatment period and a 1 week follow-up period that ended with a phone call visit.

At the end of the screening period, baseline measurements were conducted for orthostatic symptoms (as measured by the OHQ, which includes both the OHSA and the OHDAS) and BP response to orthostatic challenge. Eligible patients then entered the open-label dose-titration, where they were treated with droxidopa and titrated to effect. Dose titration began at 100 mg three times daily (TID) (upon awakening and every 4 hours thereafter with half a glass of water) of droxidopa with up-titration in 100-mg tid increments until one or more of the following criteria were met (dose-escalation stopping rules):

1. The patient became both asymptomatic (i.e., a score of "0" on Item 1 of the OHSA) and had an improvement in standing SBP of at least 10 mmHg relative to Baseline (all measurements made 3 minutes post-standing);
2. The patient had a sustained* SBP of greater than 180 mmHg or DBP of greater than 110 mmHg after 3 minutes of standing or after 5 minutes of sitting (i.e., 8 minutes poststanding), OR a sustained SBP greater than 180 mmHg or DBP greater than 110 mmHg measured in the supine (head and torso elevated at approximately 30° from horizontal) position;
3. The patient was unable to tolerate side effects believed to be related to the study drug;
4. The patient reached the maximum dose of 600 mg tid (1800 mg/day) droxidopa.

*Definition of sustained: 3 consecutive measurements of SBPs > 180 mmHg, or DBPs > 110 mmHg, in any orthostatic test position (supine, standing, or sitting) observed during three standing tests conducted over a 1-hour timeframe.

This study titration used a composite parameter to determine if patients were responders to droxidopa therapy, which identified a response to treatment as:

1. A change in symptoms of NOH, as indicated by an improvement of at least 1 unit on Item 1 of the OHSA (dizziness); and
2. An improvement in SBP of at least 10 mmHg at 3 minutes post-standing.

During each titration visit, patients were required to undergo an orthostatic standing test (OST) which was conducted approximately 3 hours after their morning dose. Following the OST, the patients completed OHSA Item 1 which was modified to direct the patient to rate their symptoms acutely at the time of the standing test.

Patients who were defined as being responders to open-label droxidopa treatment (by both BP and symptomatic improvement) were entered into the washout period and subsequently randomized into the double-blind treatment period at the highest tolerated dose. Non-responders were not entered into the double-blind treatment period of the study.

The next visit that followed the washout period was Visit 4, the randomization visit. The following procedures were conducted: the OHQ (which includes both the OHSA and the OHDAS); the CGI-S and CGI-I scales; a 12-lead ECG; and clinical laboratory tests. In addition, AEs, concomitant medications, and vital signs were recorded and blinded study drug was dispensed. All patients who continued to demonstrate a symptomatic benefit (change of ≥ 1 unit in Item 1 of the OHSA compared to Baseline) were randomized in a 1:1 ratio through a central Interactive Voice Randomization System (IVRS) to either droxidopa or placebo at the individualized dose determined during the titration period. Patients were instructed to return 7 days (+2 day window) after the Randomization Visit for Visit 5 (End of Study). Patients were required to complete the

OHQ evaluation at Baseline, Visit 4, and Visit 5. Global assessment evaluations using the CGI-S and CGI-I instruments were completed by the patient as well as the clinician at Baseline (CGI-S only), at Visit 4 and at Visit 5.

Patients were instructed to report the severity of the symptoms over the previous week.

> **Reviewer's Comments: Instructing patients to report the symptoms over the previous week could be problematic because of difficulty with remembering. Additionally, if symptoms changed over the week it would be difficult to decide upon what how to answer the questions. Moreover, the 11-point scales (see Figure 8) included anchors for only 0 (none) and 10 (worst possible), and did not include anchors in the middle of the scale (i.e., mild, moderate, severe) that could have improved consistency in patients' responses. These issues would probably bias results against droxidopa by creating noise and possibly lead to an underestimation of the difference in effect between placebo and the drug.**

Enrollment Criteria: Patients had a screening visit. To enroll, the patient had to have the clinical diagnosis of OH associated with Primary Autonomic Failure (PD, MSA and PAF), Dopamine Beta Hydroxylase Deficiency or Non-Diabetic Autonomic Neuropathies; and have a documented fall in systolic BP of at least 20 mmHg, or in diastolic BP of at least 10 mmHg, within 3 minutes after standing. Patients could not be on vasoconstricting agents or anti-hypertensive medications except for short-acting anti-hypertensive medications at bedtime. Other prohibited medications included non-selective MAOIs, tricyclic antidepressants, ergotamine derivatives (except if anti-Parkinsonian medication), oxytoxicin, reserpine derivatives, phenothiazine or butyrophenone tranquilizers, sedating H1-type antihistamines, clozapine and other major tranquilizers. To enroll, the patients could not have sustained severe hypertension (BP ≥ 180/110 mmHg in the sitting position), a significant cardiac arrhythmia, diabetes mellitus or a significant medical condition or illness aside from the disease underlying the orthostatic hypotension.

> **REVIEWER'S COMMENT(S): These criteria for the most part reflect the population in which this drug may be indicated for use. I have a concern that there could be off-label use in a much broader patient population if droxidopa is approved. If so, there could be unexpected ramifications regarding safety since the safety in these patients was not explored; e.g., diabetics, dialysis patients and patients with postural orthostatic tachycardia**.

All anti-Parkinsonian drugs were permitted during the study, provided that patients had been taking a stable dose and there had been no change in their drug treatment within 2 weeks of the start of study drug administration.

REVIEWER'S COMMENT(S): It should be noted that theoretically, some Parkinson's disease drugs (the dopamine decarboxylase inhibitors) should interfere with the conversion of droxidopa to norepinephrine. It was a risk to include patients who take these drugs.

All drugs for OH (with the exception of vasoconstricting agents) were permitted during the study, provided that patients had been taking a stable dose and there had been no change in their drug treatment within 2 weeks of the start of study drug administration. The dose and frequency of these other treatments for OH must have remained stable throughout the conduct of the study.

The study did not control for the variability of non-pharmacologic interventions associated with OH management (i.e., salt intake, water intake, wearing of compression stockings).

REVIEWER'S COMMENT(S): There was no documentation of these other pharmacologic interventions. If unblinding had occurred, these interventions could have been manipulated and there would have been no record of it.

Primary Efficacy Variable: The primary efficacy variable was the relative change in the mean score of the composite Orthostatic Hypotension Questionnaire (OHQ) 7 days following the randomization to treatment with droxidopa or placebo. The instructions for OHQ are included in Table 2. The OHQ questions are included in Figure 8 and Figure 9. Note that the OHQ is comprised of two questionnaires; the Orthostatic Hypotension Symptom Assessment (OHSA) which has 6 items that pertain to symptoms and the Orthostatic Hypotension Daily Activity Scale (OHDAS) which has 4 items that pertain to the perceived ability to stand and walk. To score the OHQ, each subscale is averaged and then the OHSA and OHDAS are averaged. In scoring the scale this way, the OHDAS questions are weighted more heavily than the OHSA questions.

The primary efficacy variable was changed mid-study from Item 1 of the OHSA (dizziness, lightheadedness, feeling faint or feeling like you might black out) to the OHQ composite score. This change was made following an informative analysis from a separate study (Study 302). Based on the findings of Study 302, the sponsor resized the study in order to achieve adequate power. According to the sponsor, all study participants remained blinded to all study results at the time of these changes.

The primary analysis of the primary efficacy endpoint (OHQ composite score), droxidopa and placebo groups were compared using an analysis of covariance (ANCOVA). The change from Randomization (Visit 4) to End of Study (Visit 5) was the dependent variable, with the value at Randomization as the covariate and treatment group as the main effect. The assumptions for the ANCOVA (independence, constant

variance, and normality of the residuals) were to be assessed (they were assessed and the assumptions were met).

The full analysis set (FAS), defined as all subjects who were randomized and received at least one dose of the test drug, was used for the primary analysis. Missing data were imputed using the Last Observation Carried Forward (LOCF) method. Since there was only one assessment of the OHQ following randomization, patients who had a missing value at End of Study (Visit 5) were assumed to have a change from randomization equal to 0.

In order to assess the impact of missing data on the primary analysis, the primary efficacy analysis was repeated excluding patients who had missing data for the primary endpoint. The order of the secondary analyses was prespecified. The order is presented in the results section.

Table 2: Instructions for OHQ

The following instructions on filling out the OHQ and the different components of the OHQ were located in Module 5, Section 5.3.5.1, Study 301, part 16.1.1 titled, "Protocol and Protocol Amendments", p. 69-71/494: We are interested in measuring the symptoms that occur because of your problem with low blood pressure (orthostatic hypotension) and the degree that those symptoms may interfere with your daily activity. It is important that we measure the symptoms that are due ONLY to your low blood pressure, and not something else (like diabetes or Parkinson's disease). Many people know which of their symptoms are due to low blood pressure. Some people who have recently developed problems with low blood pressure may not easily distinguish symptoms of low blood pressure from symptoms caused by other conditions. In general, symptoms of your low blood pressure problem will appear either upon standing or after you have been standing for some time, and will usually improve if you sit down or lie down. Some patients even have symptoms when they are sitting which might improve after lying down. Some people have symptoms that improve only after sitting or lying down for quite some time. Please answer the questions on the following pages keeping in mind that we want to know only about those symptoms that are from your problem with low blood pressure.

Figure 8: OHSA Portion of OHQ

I. **The Orthostatic Hypotension Symptom Assessment (OHSA)**

Please circle the number on the scale that best rates how severe your symptoms from low blood pressure have been ***on the average*** over the past week. Please respond to every symptom. If you do not experience the symptom, circle zero (0). PLEASE RATE THE SYMPTOMS THAT ARE DUE ONLY TO YOUR LOW BLOOD PRESSURE PROBLEM.

1. Dizziness, lightheadedness, feeling faint, or feeling like you might black out

None 0 1 2 3 4 5 6 7 8 9 10 Worst Possible

2. Problems with vision (blurring, seeing spots, tunnel vision, etc.)

None 0 1 2 3 4 5 6 7 8 9 10 Worst Possible

3. Weakness

None 0 1 2 3 4 5 6 7 8 9 10 Worst Possible

4. Fatigue

None 0 1 2 3 4 5 6 7 8 9 10 Worst Possible

5. Trouble concentrating

None 0 1 2 3 4 5 6 7 8 9 10 Worst Possible

6. Head/neck discomfort

None 0 1 2 3 4 5 6 7 8 9 10 Worst Possible

Figure 9: OHDAS Part Of OHQ

II. The Orthostatic Hypotension Daily Activity Scale (OHDAS)

We are interested in how the low blood pressure symptoms you experience affect your daily life. Please rate each item by circling the number that best represents how much the activity has been interfered with *on the average* over the past week by the low blood pressure symptoms you experienced.

If you cannot do the activity for reasons other than low blood pressure, please check the box at right.

		CANNOT DO FOR OTHER REASONS
1. Activities that require standing for a short time		
No Interference 0 1 2 3 4 5 6 7 8 9 10	Complete Interference	☐
2. Activities that require standing for a long time		
No Interference 0 1 2 3 4 5 6 7 8 9 10	Complete Interference	☐
3. Activities that require walking for a short time		
No Interference 0 1 2 3 4 5 6 7 8 9 10	Complete Interference	☐
4. Activities that require walking for a long time		
No Interference 0 1 2 3 4 5 6 7 8 9 10	Complete Interference	☐

Reviewer's Comment: According to Dr. Elektra Papadopoulos of the Study Endpoints and Labeling Development (SEALD) team, the content validity of the OHQ is not well supported by the data provided in the submission.

The conclusion of the SEALD review was that the OHSA Item 1 has adequate content validity and therefore can be relied upon to characterize

the benefit of droxidopa. This will be discussed at greater length in Section 6.

Secondary Efficacy Variables: The key secondary efficacy variables were evaluated using a hierarchical testing procedure:

- Systolic blood pressure (SBP) and diastolic blood pressure (DBP) at 3 minutes post standing;
- Global assessment evaluations using the clinician-recorded and patient-recorded Clinical Global Impressions-Severity (CGI-S) and Clinical Global Impressions-Improvement (CGI-I) scales;
- Symptom and activity measurements using the individual and composite scores of the OHSA and OHDAS subcomponents of the OHQ.

CGI-S and CGI-I

Global assessment evaluations using the clinician- and patient-rated CGI-S and CGI-I scales were summarized by randomized treatment group and visit. According to the sponsor, the CGI-S and CGI-I are widely used scales. The CGI-S is a 7-point scale ranging from a score of 1 (normal; no symptoms) to 7 (severe symptoms). A reduction in score over a period of time is considered an improvement in symptoms. The CGI-I is a 7-point scale ranging from a score of 1 (very much improved) to 7 (very much worse), with no change in the middle, and assesses the improvement in relation to the Baseline evaluation.

The CGI-S and CGI-I are general tests of clinical illness that are not disease-dependent and while the sponsor claims that they were adapted to NOH, it is unclear, given the spectrum of concomitant conditions and medications, how the scale could distinguish between NOH and other disease related symptoms. Therefore, the results of these tests may not be very informative.

See Appendix A to see these instruments as the investigators and patients saw them.

The Orthostatic Standing Test

The Orthostatic Standing Test (OST), conducted at each visit, consisted of supine (head and torso elevated at approximately 30° from horizontal) SBP, DBP, and heart rate (HR) measurements at 10 minutes, 5 minutes, and immediately prior to standing, and 3 minutes post-standing; a final measurement was taken after patients were seated for 5 minutes after the standing test was complete (standing +8 minutes). The change from pre-standing to standing +3 minutes and +8 minutes post-standing (3 minutes standing and 5 minutes seated) were summarized by treatment group and visit.

Safety

Safety evaluations were based on physical examinations, vital signs (with a particular interest in supine BPs measured during standing tests), ECG, blood and urine safety laboratory tests, deaths, SAEs and nonserious AEs.

REVIEWER'S COMMENT(S):

Not having a fixed dose trial makes it more difficult to determine the effect size per dose.

Having the patients get titrated to an effective dose and eliminating non-responders was a strategy to enrich the population of participants with those who were more likely to respond favorably to being on drug, and those who were able to tolerate the drug. This was a clever way to improve the efficiency of the trial. On the other hand, it should almost guarantee success in such a short trial.

Also, with such a short trial, any diminution of effectiveness with time would probably not be demonstrated.

On the safety side of things, there were no patients who were naive to droxidopa during the length of the trial since all patients went through the titration phase. Any delayed onset signal (carry-over effect) might appear in the double-blind phase placebo group as often as in the double-blind droxidopa group. Therefore, this design would tend to obscure safety signals.

An additional problem with the safety assessment was that no patients were allowed to lie flat while on study making it impossible to evaluate the full magnitude of supine hypertension.

Results:
Subject Demographics:

When looking at the demographic characteristics (See Table 3) the most notable finding is the absence of ethnic and racial diversity in the FAS. I decided to investigate the racial/ethnic distribution in Parkinson's disease in the U.S. In a 2003 article by Van Den Eeden et al, published in the American Journal of Epidemiology[15] it was suggested that Parkinson's is most common in Hispanics (age and gender adjusted rate per 100,000 was 16.6, 95% CI: 12.0, 21.3), followed by non-Hispanic Whites (13.6, 95% CI: 11.5, 15.7), Asians (11.3, 95% CI: 7.2, 15.3), and Blacks (10.2, 95% CI: 6.4, 14.0). The lack

of representation of patients who were Hispanic, Asian or Black is concerning vis a vis the generalizability of the findings both for efficacy and safety.

Most demographic characteristics were similar between the double-blind placebo and droxidopa treatment groups. The demographic characteristics of the patients who received open-label (OL) treatment but were not entered into the double-blind phase (i.e., subjects who did not respond to and/or tolerate droxidopa) were similar to those of the randomized population, with the exceptions of age (the OL population were a mean of almost 10 years older than the patients that were randomized), gender (the OL population was comprised of more men than women whereas the randomized population was more evenly distributed), and geographic region (in the OL population was equally distributed between the United States (US) and outside US (OUS), whereas the randomized population was more predominantly OUS (approximately 60:40). Having more OUS data often raises concerns about study conduct, particularly when results are more favorable in the OUS compared to the US population which, in fact, occured in Study 301. For this reason a Department of Scientific Investigations (DSI) consult was obtained. There were no serious conduct issues identified during these investigations.

There were few differences in disease characteristics between the randomized groups. One notable difference is that there were more patients with Parkinson's disease in the group randomized to droxidopa when compared to placebo (43.2% vs. 38.3%). As shown later, the patients with PAF and MSA were more likely than patients with Parkinson's disease to respond to droxidopa. Therefore, this imbalance between the treatment groups in numbers of patients with Parkinson's disease ended up biasing the results against droxidopa. On a reassuring note, the level of disease severity entering the study was similar between the placebo and droxidopa treatment groups. At Visit 2, prior to titration, the mean Baseline OHQ composite scores were similar; 5.62 and 5.96 units for the placebo and droxidopa groups, respectively. The mean SBP post-standing 3 minutes was 90.7 and 90.8 mmHg for the placebo and droxidopa groups, respectively. Concomitant medication use was typical for the patient population of the study. There was no clinically meaningful difference in concomitant medication use by Anatomical Therapeutic Chemical (ATC) class or drug name observed between patients in the open-label titration phase or between the placebo and droxidopa treatment groups in the double-blind phase.

Table 3: Demographics of Study 301

	Open-Label Phase[1] (N=101)	Double-Blind Phase	
		Placebo (N=81)	Droxidopa (N=81)
Sex [n (%)]			
Male	64 (63.4)	43 (53.1)	41 (50.6)
Female	37 (36.6)	38 (46.9)	40 (49.4)
Race [n (%)]			
White	99 (98.0)	76 (93.8)	81 (100.0)
Black/African American	2 (2.0)	1 (1.2)	0
Asian	0	1 (1.2)	0
Hispanic/Latino	0	3 (3.7)	0
Primary Clinical Diagnosis [n (%)]			
Parkinson's Disease	45 (44.6)	31 (38.3)	35 (43.2)
Multiple System Atrophy	18 (17.8)	12 (14.8)	14 (17.3)
Pure Autonomic Failure	33 (32.7)	28 (34.6)	26 (32.1)
Dopamine Beta Hydroxylase Deficiency	0	0	0
Non-Diabetic Autonomic Neuropathy	2 (2.0)	6 (7.4)	2 (2.5)
Other Diagnosis	3 (3.0)	4 (4.9)	4 (4.9)
Age (Years) at Screening			
Mean (SD)	64.6 (15.40)	55.8 (19.94)	57.3 (16.98)
Min, Max	19, 91	18, 87	20, 84
Weight (kg)			
N	99	80	80
Mean (SD)	74.85 (15.062)	74.96 (14.413)	74.10 (14.516)
Min, Max	44.0, 113.4	47.0, 110.0	46.0, 103.0
Geographic Region [n (%)]			
US	48 (47.5)	33 (40.7)	32 (39.5)
Non-US	53 (52.5)	48 (59.3)	49 (60.5)
Baseline OHQ Composite Score			
n		79	81
Mean (SD)		5.62 (1.98)	5.96 (1.67)
Min, Max		1.2, 9.8	2.0, 9.6
Baseline SBP upon Standing +3 Minutes (mmHg)			
n		80	82
Mean (SD)		90.7 (16.83)	90.8 (15.63)
Min, Max		50, 130	45, 142

Max=Maximum; Min=Minimum; SD=Standard deviation; US=United States.
1 Patients who were titrated in the open-label phase but not randomized were included only in the open-label droxidopa column. This also includes the 6 patients who received study treatment during the open-label titration phase who were randomized but never received double-blind drug.
OHQ=Orthostatic Hypotension Questionnaire; Max=Maximum; Min=Minimum; SBP=Systolic blood pressure; SD=Standard deviation.
Source: Table 11-2, Study Report 301, section 11.2, p. 60.

Compliance

Compliance was in the 99 -100% range for both arms of Study 301.

REVIEWER'S COMMENT(S):

With a trial this short, it's not surprising that compliance is so good.

Dose
Of those randomized, the most common reason for stopping droxidopa titration was the patient becoming asymptomatic (i.e. scored "0" on Item 1 if the OHSA) and having an improvement in standing SBP of at least 10 mmHg relative to Baseline (measured 3 minutes post-standing; 99 patients [61.1%]). The second most common reason was the patient reaching the maximum titration dose (n=53 [32.7%]). Other reasons for stopping titration included sustained SBP >180 mmHg or DBP >110 mmHg (n=10 [6.2%]), or because the patient was unable to tolerate side effects (n=19 [11.7%]. The doses that were finally arrived at for the randomized patients are listed in Table 4.

Table 4: Titrated Doses (Study 301)

Dose	Placebo n	Droxidopa n
100 mg tid	5	5
200 mg tid	7	9
300 mg tid	24	11
400 mg tid	19	16
500 mg tid	9	10
600 mg tid	15	29

Source data: ISS Table 11-5

Concomitant Medications
The majority of patients in the study took concomitant medications. In the open-label phase, 208 (79.1%) patients took concomitant medications. In the double-blind phase, 61 (75.3%) placebo-treated and 63 (77.8%) droxidopa-treated patients took concomitant medications. DOPA and DOPA derivatives were the most common concomitant medications by ATC class and their use was comparable between patients in the open-label phase (45.6%) and in placebo-treated (39.5%) and droxidopa-treated patients (39.5%) in the double-blind phase. Sinemet (carbidopa/levodopa) was the most commonly used DOPA derivative, taken by 29.6% of placebo-treated and 25.9% of

droxidopa-treated patients in the double-blind phase. Mineralocorticoids (fludrocortisone) were taken by 22.2% of placebo-treated and 25.9% of droxidopa-treated patients in the double-blind phase.

REVIEWER'S COMMENT(S): Overall, concomitant medication use was typical of the patient population. The slightly decreased use of Sinemet which could potentially interfere with droxidopa (by reducing peripheral conversion of droxidopa to NE) in the droxidopa group is not ideal because it could potentially introduce bias in favor of droxidopa. As shown in Table 11, later in the review, patients who did not use DOPA decarboxylase inhibitors performed better on droxidopa than patients not on DOPA decarboxylase inhibitors. Also, fludrocortisone was given to more patients in the droxidopa group, which also could have introduced bias in favor of droxidopa. The results did not turn out to be any different for patients who took fludrocortisone. While the disparate results for patients who did not take DOPA decarboxylase inhibitors bias the results in favor of droxidopa, there were only 3 more patients in the droxidopa group who did not take DOPA decarboxylase inhibitors compared to the placebo group. It is unlikely that this altered the results significantly.

Disposition

95 patients were not randomized. The reasons for not being randomized were as follows:

- 52 patients for “treatment failure,” “titration failure,” or “failed to meet qualifications as a responder”
- 5 withdrew consent
- 12 had adverse events
- 3 did not meet entry criteria
- 16 were not randomized for other reasons (“sponsor instructed patient to skip visit 4,” “enrolled into study 303,” “randomization limit was skipped or reached”)

Of the patients randomized (164), 10 withdrew for the following reasons:

- 1 had an adverse event (droxidopa 200 mg tid)
- 1 because of investigator decision (droxidopa 200 mg tid)
- 1 withdrew consent (droxidopa 600 mg tid)
- 4 patients did not complete because of treatment failure (placebo treatment group)
- 1 protocol violation because inclusion criterion not met (placebo)
- 1 incorrect titration and withdrew consent (placebo)
- 1 used blinded investigational product during the titration period (placebo)

Efficacy Analysis

Hierarchical analysis of efficacy endpoints (outcome and statistical significance):

Primary efficacy endpoint: As shown in the applicant's table (Table 5), the droxidopa treatment group had superior results to the placebo treatment group on the OHQ (p=0.003). However, the mean treatment difference between placebo and droxidopa (effect size) was 0.90 units favoring droxidopa on an 11-unit scale, a treatment effect that seems small. The biostatistical review agreed with the applicant's interpretation of the primary endpoint results.

Table 5: Summary of OHQ Composite Score (FAS)

	Placebo (N=80)	Droxidopa (N=82)	ANCOVA[3]
Randomization (Visit 4)			
N[4]	79	81	
Mean (SD)	4.97 (2.41)	5.11 (1.96)	
Min, Max	0.7, 9.8	0.9, 9.1	
End of Study (Visit 5)			
N	79	81	
Mean (SD)	4.04 (2.61)	3.29 (2.20)	
Min, Max	0.0, 9.8	0.0, 8.4	
Change from Randomization to End of Study			
N	79	81	0.003
Mean (SD)	-0.93 (1.69)	-1.83 (2.07)	
Min, Max	-7.5, 2.6	-6.2, 4.4	

ANCOVA=Analysis of covariance; LOCF=Last observation carried forward; OHDAS=Orthostatic Hypotension Daily Activity Scale; OHQ=Orthostatic Hypotension Questionnaire; OHSA=Orthostatic Hypotension Symptom Assessment; Max=Maximum; Min=Minimum; SD=Standard deviation.

1 OHQ composite score is the average of the OHSA and OHDAS composite scores. The OHSA composite score is the average of Items 1-6 with a score of 1 or more at the Baseline Visit. The OHDAS composite is the average of the four items from the OHDAS excluding those with a Baseline value of zero or 'cannot do for other reasons'.

2 Missing data were imputed using the LOCF method.

3 The p-value from ANCOVA model included a factor for randomized treatment along with the OHQ composite value at Randomization as a covariate.

4 The data represent the results for patients in the Full Analysis Set with measurements at Baseline, Randomization, and at End of Study; there were 2 patients (1 randomized to placebo and 1 to droxidopa treatment) without Baseline measurements that are not represented as per the statistical analysis plan.

Source: Table 11-5 in the Study Report for Study 301, section 11.4.1.1, p. 63

The FAS with missing data excluded was not appreciably different. (-0.92, p=0.002). Results of analyses performed on the Per Protocol Set were similar to those of the FAS.

An interesting finding is that the improvement in OHQ score in the placebo group increases over time regardless of being off drug for another week (Table 6). By the End of Study, which occurred one week after the randomized period, the mean OHQ test score for the placebo treatment group was 4.04, compared to 5.62 at their baseline (an improvement of 1.58 units). In fact, all of the items in the OHQ improved during the randomized period as shown in Table 7 and in Table 8. The droxidopa treatment group had an even larger improvement. While the droxidopa improvement (-2.67) is expected if we assume the drug is effective, the placebo improvement is not. Possible reasons for improvement in the placebo group include: 1) placebo effect; 2) droxidopa given during the titration phase is continuing to exert a positive effect on symptoms; 3) the effects of being in a clinical trial, i.e., sleeping with head of bed elevated, getting more exercise, etc.

Table 6: Change in OHQ scores between Baseline and Randomization and between Baseline and End of Study by Treatment Group

	Change in OHQ score from baseline to randomization (after washout)	Change in OHQ score form baseline to End of Study
Placebo	-0.65	-1.58
Droxidopa	-0.85	-2.67

Table 7: Summary of the OHSA (FAS with LOCF)

OHSA Item Symptom	Placebo, Mean (SD) N=80			Droxidopa, Mean (SD) N=82			ANCOVA[2]
	Randomization	End of Study	Δ	Randomization	End of Study	Δ	
Item #1 (n)	80	80	80	82	82	82	
Dizziness	5.4 (2.88)	4.3 (3.10)	-1.1 (2.58)	5.4 (2.46)	3.0 (2.67)	-2.4 (3.20)	<0.001
Item #2 (n)	80	80	80	82	82	82	
Vision	3.8 (3.14)	3.0 (3.15)	-0.7 (2.25)	3.4 (2.58)	1.9 (2.28)	-1.6 (2.81)	0.013
Item #3 (n)	80	80	80	82	82	82	
Weakness	5.0 (3.02)	4.1 (2.93)	-0.9 (2.34)	5.2 (2.23)	3.3 (2.29)	-1.9 (2.54)	0.007
Item #4 (n)	80	80	80	82	82	82	
Fatigue	5.5 (2.81)	4.3 (2.88)	-1.2 (2.51)	5.3 (2.35)	3.4 (2.48)	-1.9 (2.57)	0.030
Item #5 (n)	80	80	80	82	82	82	
Concentration	4.1 (2.86)	3.2 (2.80)	-0.9 (2.15)	3.5 (2.44)	2.6 (2.38)	-0.9 (1.89)	0.355
Item #6 (n)	80	80	80	82	82	82	
Head/Neck Discomfort	3.5 (3.06)	2.7 (2.74)	-0.8 (2.36)	3.6 (2.69)	2.6 (2.47)	-1.0 (2.28)	0.975
Composite (n)	79	79	79	81	81	81	
Items 1-6	4.70 (2.379)	3.75 (2.520)	-0.95 (1.901)	4.60 (2.013)	2.93 (2.084)	-1.68 (2.125)	0.010

ANCOVA=Analysis of covariance; Δ=Change; LOCF=Last observation carried forward; OHSA=Orthostatic Hypotension Symptom Assessment; SD=Standard deviation.
1 Missing data were imputed using the LOCF method.
2 p-values from non-parametric ANCOVA (Items 1, 2, 5, and 6) or parametric ANCOVA (Items 3, 4, and the OHSA composite score). ANCOVAs were adjusted for the covariate respective OHSA Item score at Randomization.

Source: Study report for study 301, Table 11-7, section 11.4.2.1.1, p. 66

Table 8: Summary of the OHDAS (FAS with LOCF)

OHDAS Item Symptom	Placebo, Mean (SD) N=80			Droxidopa, Mean (SD) N=82			ANCOVA[2]
	Randomization	End of Study	Δ	Randomization	End of Study	Δ	
Item #1 (n)	80	80	80	82	82	82	
Standing Short Time	4.6 (2.99)	3.8 (2.94)	-0.8 (2.60)	5.0 (2.68)	3.1 (2.59)	-1.9 (2.75)	0.003
Item #2 (n)	79	79	79	81	81	81	
Standing Long Time	5.9 (3.19)	4.9 (3.40)	-1.0 (2.11)	6.4 (2.54)	4.0 (2.79)	-2.3 (2.58)	0.001
Item #3 (n)	80	80	80	82	82	82	
Walking Short Time	4.4 (3.08)	3.8 (2.98)	-0.6 (2.37)	4.7 (2.71)	3.0 (2.74)	-1.7 (2.55)	0.009
Item #4 (n)	78	78	78	78	78	78	
Walking Long Time	5.8 (3.41)	4.8 (3.49)	-1.1 (2.19)	5.8 (2.52)	4.0 (3.00)	-1.8 (2.52)	0.007
Composite (n)	79	79	79	81	81	81	
Items #1-4	5.24 (2.844)	4.33 (2.976)	-0.92 (1.816)	5.62 (2.296)	3.65 (2.577)	-1.98 (2.310)	0.003

ANCOVA=Analysis of covariance; Δ=Change; LOCF=Last observation carried forward; OHDAS=Orthostatic Hypotension Daily Activity Scale; SD=Standard deviation.

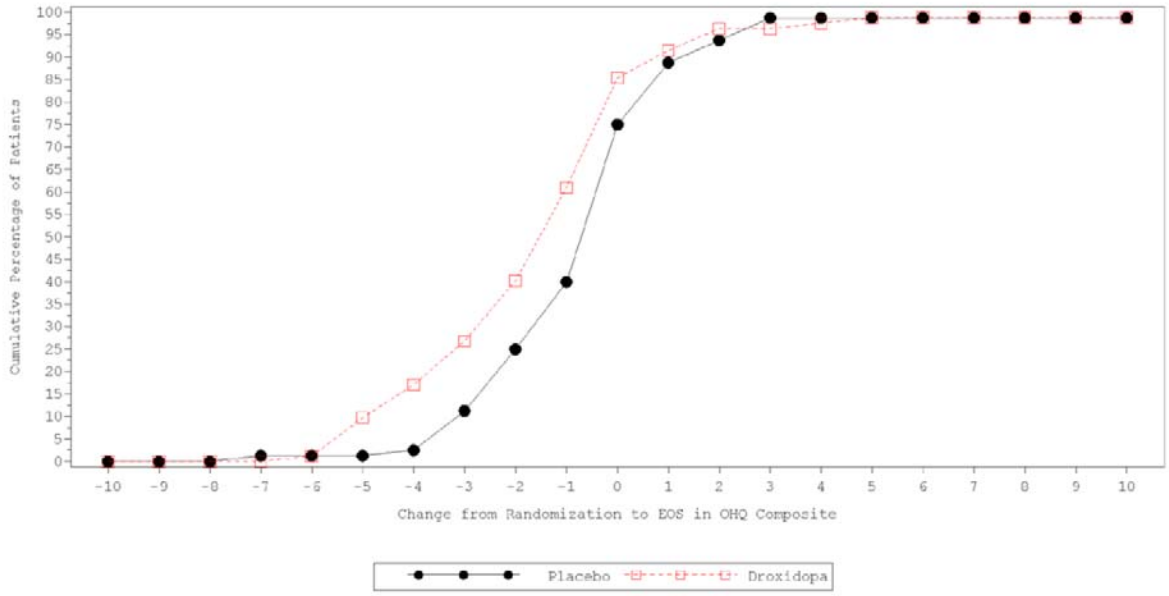
1 Missing data were imputed using the LOCF method.

2 p-values from non-parametric ANCOVA (Items 1 and 4) or parametric ANCOVA (Items 2, 3, and the OHDAS composite score). ANCOVAs were adjusted for the covariate respective OHDAS Item score at Randomization.

Source: Study report for study 301, Table 11-8, section 11.4.2.1.2, p. 68

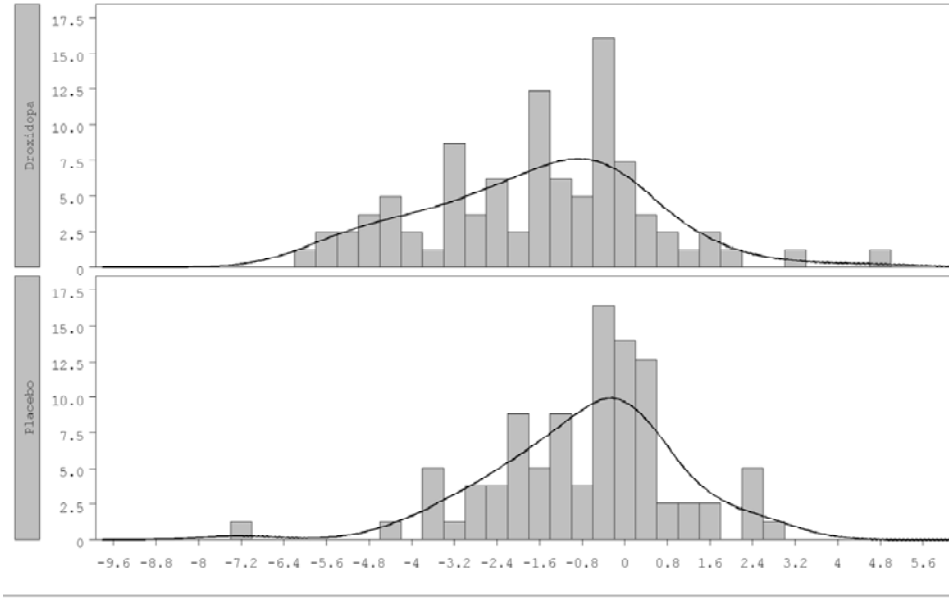
Figure 10 displays the cumulative distribution of results across the possible differences in OHQ between randomization and end of study. It shows that subjects in both groups generally improved post-randomization (the distribution is shifted to the left of zero). It also shows that at the extreme levels of improvements, the patients were more likely to be on drug than placebo. It can also be seen that for the few patients who didn't improve, there was almost equal chance of being on drug as placebo. The same data is shown in Figure 11 in a histogram (bin) format.

Figure 10: OHQ Composite Cumulative Distribution Function (FAS)



Source: Figure 4.1 in Clinical Overview (2.5) p. 27/61

Figure 11: Summary of Orthostatic Hypotension Questionnaire Composite Score



Note: Line plotted represents normal kernel density estimates.
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Change in Endpoint

The primary efficacy endpoint of Study 301 was amended because of the efficacy outcome data and post-hoc analyses from Study 302. Study 302 lost on the same primary efficacy endpoint that was originally prespecified for Study 301: OHSA Item I (dizziness, lightheadedness, feeling faint or feeling like you might black out), but was found to be superior to placebo in a post-hoc analysis on the OHQ composite. The OHQ is comprised of the OHSA composite that queries a variety of symptoms and the OHDAS that queries the ability to stand and walk. The sponsor selected the OHQ composite as the new primary efficacy endpoint for study 301 stating that they considered it to be a more comprehensive measure of clinical efficacy than the OHSA Item 1.

A protocol amendment providing for this change was submitted to the droxidopa IND on December 15, 2009 (Serial Number 061). The FDA provided final comments and recommendations regarding the change in a letter dated January 20, 2010. The Sponsor changed the primary efficacy endpoint after a majority of patients (116) had been enrolled in the double-blind period. The sample size was also increased (from 118 patients to 150 patients) at the time of the change in the primary endpoint.

Although there might be some concerns about changing an endpoint after almost all planned subjects have completed a trial, it is very reassuring that study 301 would have won on its primary endpoint if it had not been changed at the time of the last patient

completion prior to the amendment (September 28, 2009). The results are shown below:

	N	mean	std
Droxi:	64	-2.5	3.3
Placebo:	62	-1.5	2.4

Rank sum test p-value: 0.01
Source: Jialu Zhang, PhD, statistician FDA

Study 301 would also have won on the OHQ if it had been stopped prior to the amendment (before increasing the size).

Secondary efficacy endpoints:
All secondary efficacy endpoints were evaluated using the FAS with missing values imputed using LOCF.

In order to control the overall type I error, statistical significance of the primary and key secondary efficacy endpoints was evaluated using a hierarchical testing procedure. The hierarchy of endpoints was defined as follows (using FAS with LOCF):

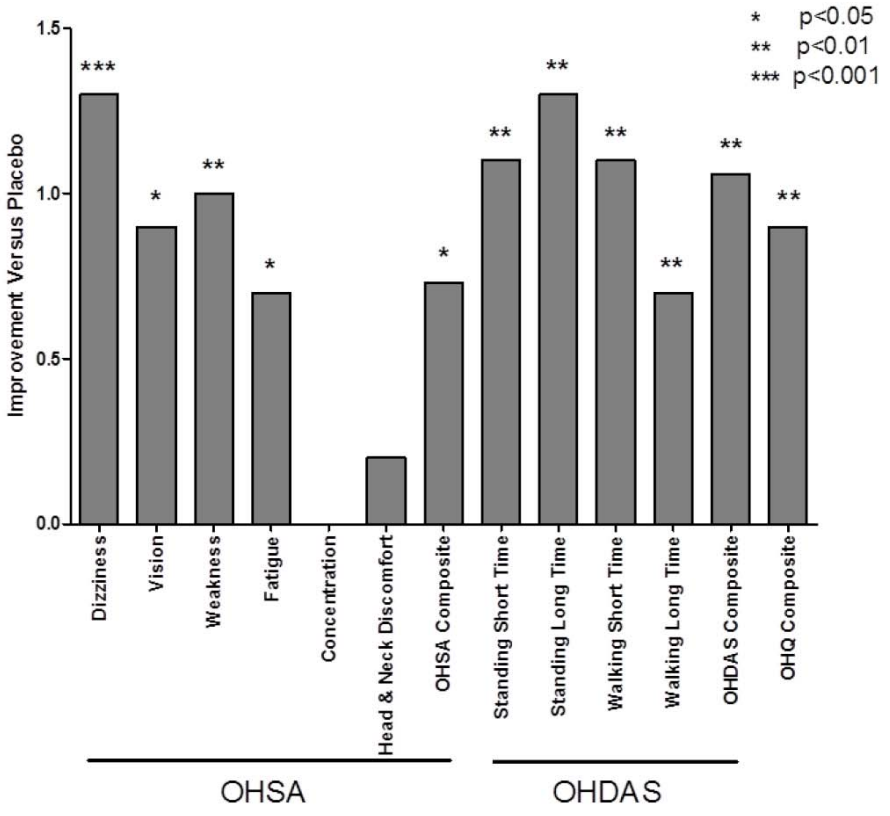
1. The change in OHDAS composite score for Items 1-4 (calculated as the arithmetic average of Items 1-4) from Randomization to End of Study (p=0.003);
2. The change in OHSA composite score for Items 1-6 (calculated as the arithmetic average of Items 1-6 with a Baseline score greater than 0) from Randomization to End of Study (p=0.010);
3. The change in OHDAS Item 1 (standing short time) from Randomization to End of Study (p=0.003);
4. The change in OHDAS Item 3 (walking short time) from Randomization to End of Study (p=0.009);
5. The change in OHSA Item 1 (dizziness, lightheadedness, feeling faint or feeling like you might black out) from Randomization to End of Study (p<0.001);
6. Trend was favorable for droxidopa but there was no statistically significant difference in the percent of responders by the patient-rated CGI-S

Because the analysis performed for the 6th secondary endpoint did not show statistically significant results, no formal statistical analyses were performed for the other secondary endpoints in the hierarchy.

Exploration of the Performance of the Individual Items of the OHSA and OHDAS

As shown in Figure 12, most of the items of the OHQ showed an improvement in the droxidopa arm that was nominally statistically significant. Concentration and Head & Neck Discomfort were the exceptions.

Figure 12: Treatment Difference in the Change from Randomization to the End of Study (FAS)



ANCOVA=Analysis of covariance; OHDAS=Orthostatic Hypotension Daily Activity Scale; OHQ=Orthostatic Hypotension Questionnaire; OHSA=Orthostatic Hypotension Symptom Assessment.

Note: The differences between placebo and droxidopa with respect to changes from Randomization were evaluated using an ANCOVA model including a factor for randomized treatment along with the OHSA composite value at Randomization as a covariate.

Source: Figure 4.2 in Clinical Overview (2.5) p. 28/61

Evaluation of the OHQ composite score and the OHSA and OHDAS individual items and composite scores with missing data excluded yielded similar results compared with the LOCF analysis.

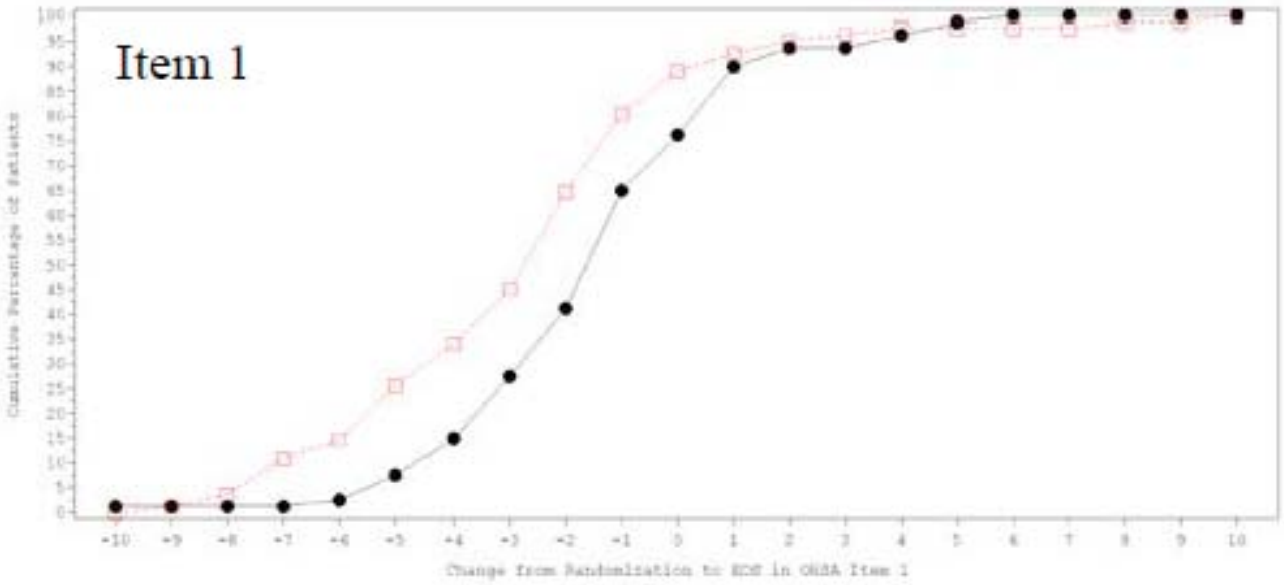
Orthostatic Hypotension Symptom Assessment (OHSA) Item 1

According to the Study Endpoints and Labeling Development (SEALD) review by Dr. Elektra Papadopoulos, the content validity of the OHQ is not well supported by the data that was provided in the submission. The OHSA Item 1, however, which was the original primary efficacy endpoint is satisfactorily supported and appears to be a more appropriate endpoint. In study 301, the OHSA Item 1 showed improvement in the droxidopa group compared to the placebo group (mean difference of 1.3). In fact, the p value was <0.001. As shown in Figure 13, there is nearly uniform improvement in the OHSA Item 1 compared to placebo and compared to baseline across most of the

cumulative distribution curve. The curves separate more as the magnitude of the change from baseline increases up to a -5 change.

REVIEWER'S COMMENT(S): This trend (separation of curves as the magnitude of change from baseline increases) supports the findings that there is a salutary effect of droxidopa on the OHSA Item 1.

Figure 13: OSHA Item 1 Cumulative Distribution Function (FAS)



Source: ISE Figure 4-4

Clinical Global Impressions –Severity and Clinical Global Impressions- Improvement (patient and clinician ratings)

Trends toward improvement from Baseline to End of Study were observed for both the Clinician- and Patient-rated CGI-S and CGI-I assessments in both groups; On the CGI-S there was improvement by at least 1 point in 58.5% and 46.3% of patients following droxidopa and placebo treatment, respectively (FAS, LOCF). Overall, there was no statistical difference observed between the droxidopa and placebo groups using Fisher's exact test.

REVIEWER'S COMMENT(S): Ideally, one would have liked to have seen an improvement in these scales, particularly the CGI-S. The CGI-I relies on long-term memory and therefore, lack of significant changes on this scale are less indicative of absence of effect. Nevertheless, these are general scales and improvement and decline on them may reflect other comorbid conditions and effects of other life events. Therefore, taken alone, lack of statistical significance on these scales should not be counted against droxidopa.

Standing Systolic Blood Pressure Changes

The sponsor's two analyses were as follows:

1. The first analysis was the difference in the delta between Randomization and End of Study in standing SBP compared with placebo using ANCOVA testing. The mean change in standing SBP was 11.2 mmHg following treatment with droxidopa compared with 3.9 mmHg following treatment with placebo ($p<0.001$; a difference between placebo and droxidopa of 7.3 mmHg favoring droxidopa). The results show that droxidopa increases standing systolic blood pressure at 3 minutes after standing compared to placebo after one week of treatment (Table 9, Figure 14). Figure 15 depicts the cumulative distribution of SBP change at 3 minutes after standing.

   REVIEWER'S COMMENT(S): Table 9 shows that SBP does not return completely to baseline after washout and that the SBP does not rise as high during the randomization period as it did during the titration period for the patients on droxidopa. This decline in SBP compared to the end of titration period could indicate that there is already a down-regulation of norepinephrine receptors by the end of the double-blind period, a down-regulation of adrenal gland production of catecholamines, an increase in the catecholamine metabolic pathway or some other adaptation that blunts the drug effect.

2. The second analysis was the change from pre-standing to post-standing systolic BP at End-of-Study between placebo and droxidopa using ANCOVA testing. The difference in pre- to post- standing systolic blood pressure from randomization to the end of the DB study period was not statistically significant between treatment groups. This analysis indicates that the change in SBP that occurs with droxidopa is an overall increase in both standing and supine BP. As shown in Table 10, the orthostatic change in SBP is not significantly altered with treatment.

Table 9: Summary of Systolic Blood Pressure (mmHg) During Orthostatic Standing Test (Full Analysis Set)

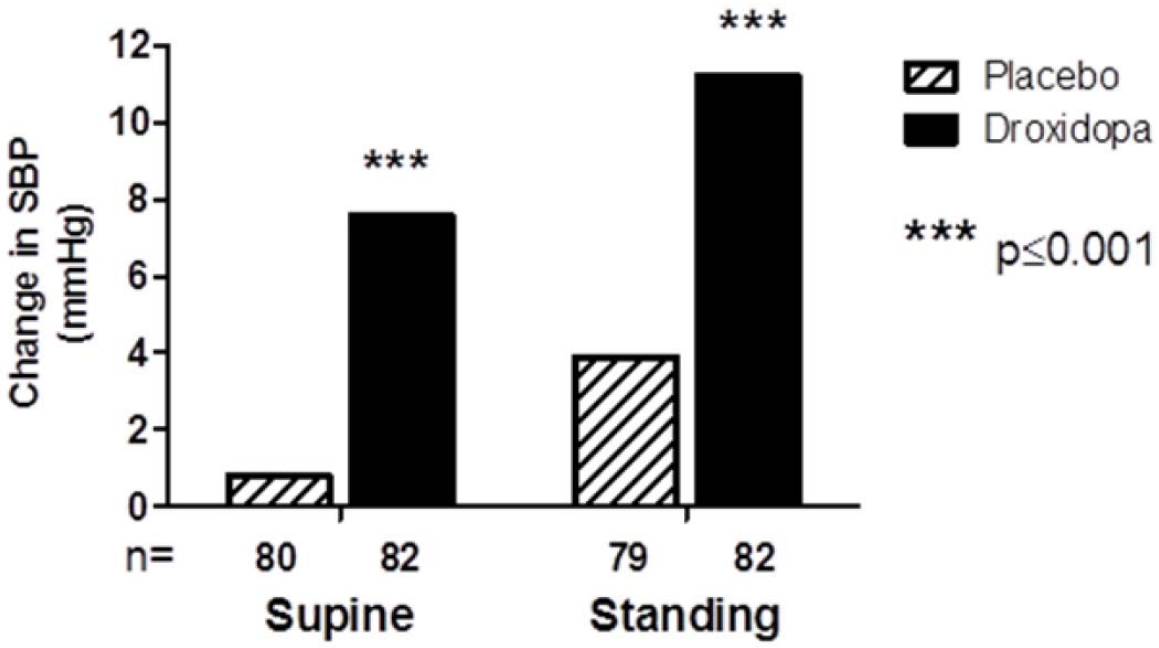
SBP upon Standing +3 Minutes (mmHg)	Placebo N=80			Droxidopa N=82		
	Result	Change from Baseline	Change from Randomization	Result	Change from Baseline	Change from Randomization
Baseline (n)	80			82		
Mean (SD)	90.7 (16.83)	--	--	90.8 (15.63)	---	--
Min, Max	50, 130			45, 142		
End of Titration (n)	79	79		82	82	
Mean (SD)	114.8 (21.62)	24.1 (18.81)	--	113.2 (15.26)	22.4 (13.08)	--
Min, Max	68, 204	-7, 123		78, 151	-22, 65	
Randomization (n)	80	80		82	82	
Mean (SD)	98.2 (22.10)	7.5 (15.48)	--	96.2 (19.35)	5.4 (16.41)	--
Min, Max	46, 150	-37, 48		60, 152	-38, 72	
End of Study (n)	79	79	79	82	82	82
Mean (SD)	101.8 (22.34)	11.0 (19.14)	3.9 (16.28)	107.4 (20.42)	16.6 (20.02)	11.2 (22.89)
Min, Max	60, 156	-30, 72	-60, 74	63, 158	-32, 83	-72, 64
p-value[1]					0.041	<0.001

ANCOVA=Analysis of covariance; Max=Maximum; Min=Minimum; SBP=Systolic blood pressure; SD=Standard deviation.

1 The differences between placebo and droxidopa with respect to changes from Baseline and Randomization were evaluated using non-parametric ANCOVA using Mantel-Haenszel methodology based on rank statistics adjusted for the Baseline or Randomization value as a covariate.

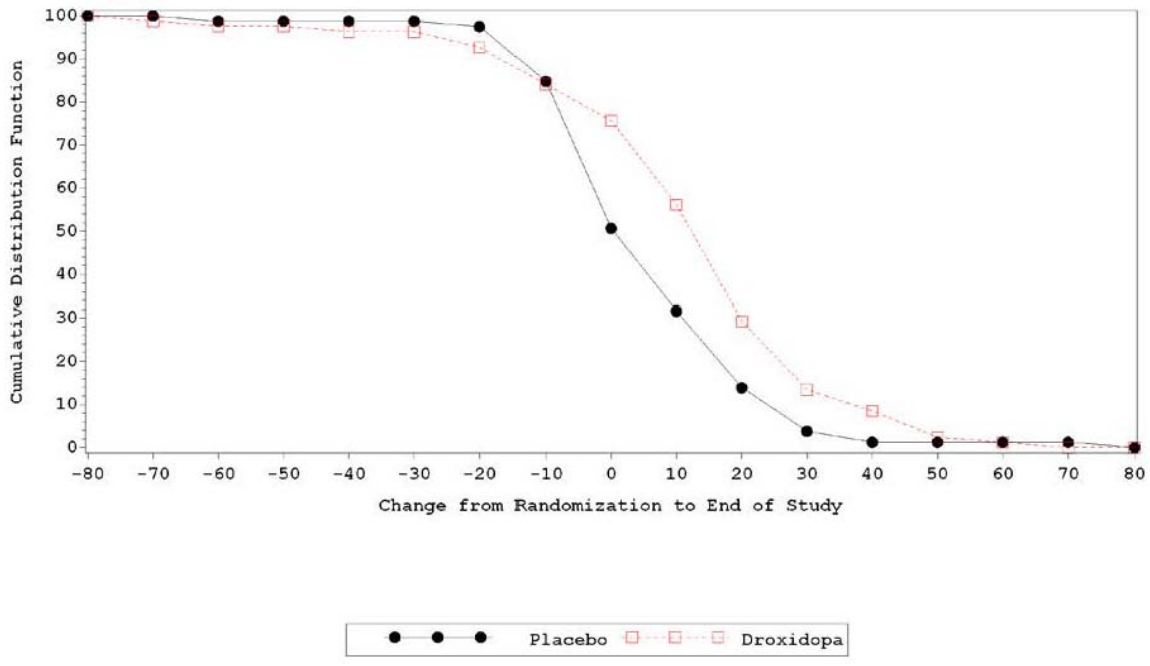
Source: Table 11-11 in Study 301 Study Report (5.3.5.1) p. 75/1440

Figure 14: Standing vs. Supine Blood Pressure from Randomization to End of Study (FAS)



Source: Figure 4-4 in Clinical Overview (2.5), p. 30/61

Figure 15: Change in 3 min Standing SBP from Randomization to End of Study (Study 301)



Source ISE: Figure 4-7

Table 10: Summary of Change from Pre-Standing to Post-Standing in Systolic Blood Pressure (mmHg) During the Orthostatic Standing Test (FAS)

Change from Pre-Standing to Standing +3 minutes (mmHg)	Placebo N=80			Droxidopa N=82		
	Result	Change from Baseline	Change from Randomization	Result	Change from Baseline	Change from Randomization
Baseline (n)	80	--	--	82	--	--
Mean (SD)	-31.7 (18.99)			-36.8 (20.03)		
End of Titration (n)	79	79	--	82	82	
Mean (SD)	-20.4 (23.97)	11.3 (19.81)		-21.0 (20.88)	15.8 (17.55)	--
Randomization (n)	80	80		82	82	
Mean (SD)	-27.0 (20.49)	4.8 (13.19)	--	-29.9 (21.60)	6.9 (16.36)	--
End of Study (n)	79	79	79	82	82	82
Mean (SD)	-23.8 (20.97)	7.7 (14.87)	2.9 (13.58)	-26.4 (24.79)	10.5 (20.42)	3.5 (17.77)
p-value[1]					0.658	0.607

ANCOVA=Analysis of covariance; SBP=Systolic blood pressure; SD=Standard deviation.
1 The differences between placebo and droxidopa with respect to changes from Baseline and Randomization were evaluated using ANCOVA model including a factor for randomized treatment along with the SBP value at Baseline or Randomization as a covariate.

Source: Table 11-12 in Study 301 Study Report (5.3.5.1) p. 76/1440

Diastolic Blood Pressure Changes

Patients receiving droxidopa experienced numerical improvements from Randomization to End of Study in standing DBP compared with placebo: a mean change in standing DBP of 5.5 mmHg (from 62.8 mmHg at Randomization to 68.3 mmHg at End of Study) following treatment with droxidopa compared with 3.4 mmHg (63.2 mmHg at Randomization to 66.2 mmHg at End of Study) to following treatment with placebo; this numerical difference was not statistically significant. The change from supine to standing DBP was 13.7 mmHg and 13.9 mmHg, respectively, for the placebo and droxidopa groups at Randomization and 10.4 mmHg and 12.2 mmHg, respectively, for the placebo and droxidopa groups at End of Study. Droxidopa does not appear to substantially affect standing diastolic BP. It also does not lessen the decrease in diastolic blood pressure that occurs upon standing in patients with orthostatic hypotension.

Subgroup Analyses
As shown in Table 11 most subgroups showed beneficial trends for droxidopa on the symptoms of NOH (as assessed by the OHQ, OHSA, and OHDAS composite scores). These include differences in gender, age, geographical region (US and non-US), primary diagnosis, concomitant drug use (DDC-Is, fludrocortisone, dopaminergic agents, droxidopa enzymatic degradation agents) dose and Baseline OH severity (by CGI-S).

There were some notable trends: the effect size in patients from OUS tended to be greater than in US patients, male patients tended to experience greater benefits than female patients, patients <65 years of age tended to experience greater benefits than those ≥65 years of age, patients with the underlying diagnoses of PAF or MSA experienced greater benefits than those with PD and patients with moderate disease responded more favorably than patients with severe disease. Given the relatively small sample sizes available for analysis and the heterogeneity of the patient populations it is difficult to draw firm conclusions from these subgroup analyses. .

Patients not on dopamine decarboxylase inhibitors appeared to show a greater improvement on droxidopa [-2.18 on droxidopa vs. -0.83 on placebo ($p < 0.001$)] than patients on these drugs [-1.28 on droxidopa vs. -1.05 on placebo ($p = 0.70$)]. This makes sense because dopamine decarboxylase agents should theoretically decrease the peripheral conversion of droxidopa to NE. It may be that use of carbidopa is the reason why patients with Parkinson's disease don't perform as well on droxidopa (compared to placebo) as patients with other underlying diseases.

Subgroup analyses by dose group on the OHQ composite score showed that greater numerical improvements in droxidopa-treated patients were seen with the three highest daily doses (400, 500, and 600 mg TID).

Table 11: Summary of OHQ Composite Score by Subgroup (Full Analysis Set)

Subgroup	Placebo, Mean (SD)			Droxidopa, Mean (SD)			ANCOVA[3]
	Randomization	End of Study	Δ	Randomization	End of Study	Δ	
Age							
<65 Years, n	46	46	46	49	49	49	
	4.70 (2.63)	3.86 (2.85)	-0.83 (1.73)	4.94 (2.09)	2.78 (2.02)	-2.16 (1.80)	<0.001
≥65 Years, n	33	33	33	31	32	31	
	5.34 (2.09)	4.30 (2.25)	-1.04 (1.73)	5.26 (1.63)	4.06 (2.27)	-1.33 (2.40)	0.498
Gender							
Male, n	41	41	41	41	41	41	
	4.73 (2.40)	3.90 (2.57)	-0.83 (1.41)	5.06 (1.83)	2.94 (1.85)	-2.13 (1.98)	0.001
Female, n	38	38	38	39	40	39	
	5.22 (2.46)	4.21 (2.68)	-1.01 (2.03)	5.07 (2.04)	3.65 (2.48)	-1.54 (2.16)	0.211
Geographical Region							
US, n	31	31	31	31	32	31	
	5.91 (2.46)	5.08 (2.99)	-0.83 (2.14)	5.65 (1.85)	4.21 (2.45)	-1.57 (2.37)	0.155
Non-US, n	48	48	48	49	49	49	
	4.36 (2.22)	3.38 (2.10)	-0.98 (1.42)	4.70 (1.90)	2.68 (1.80)	-2.02 (1.88)	0.003
Primary Diagnosis							
PD, n	30	30	30	35	35	35	
	5.09 (2.19)	4.00 (2.20)	-1.08 (1.54)	5.08 (1.75)	3.65 (2.07)	-1.43 (2.14)	0.426
MSA, n	11	11	11	14	14	14	
	6.37 (2.17)	5.76 (2.62)	-0.61 (1.00)	6.08 (1.62)	4.38 (1.97)	-1.70 (1.81)	0.087
PAF, n	28	28	28	26	26	26	
	4.88 (2.35)	3.92 (2.64)	-0.96 (2.02)	4.72 (2.13)	2.08 (1.97)	-2.63 (1.89)	0.001
NDAN, n	6	6	6	2	2	2	
	4.61 (2.83)	3.47 (3.55)	-1.13 (1.73)	6.23 (1.10)	3.23 (2.26)	-3.00 (3.36)	0.381
Other, n	4	4	4	3	4	3	
	1.30 (1.46)	1.42 (1.63)	0.11 (2.73)	2.51 (0.18)	4.19 (2.97)	0.32 (1.31)	0.225

Source: 301 Study Report, section 11.5

Table 11 (cont.): Summary of OHQ Composite Score by Subgroup (Full Analysis Set)

Subgroup	Placebo, Mean (SD)			Droxidopa, Mean (SD)			ANCOVA[3]
	Randomization	End of Study	Δ	Randomization	End of Study	Δ	
Concomitant Drug Use							
DDC-I Use, n	32	32	32	30	31	30	
	5.20 (2.23)	4.14 (2.30)	-1.05 (1.50)	5.39 (1.85)	4.24 (2.26)	-1.28 (2.06)	0.696
No DDC-I Use, n	47	47	47	50	50	50	
	4.81 (2.56)	3.98 (2.82)	-0.83 (1.87)	4.87 (1.96)	2.69 (1.96)	-2.18 (2.03)	<0.001
Fludrocortisone Use, n	16	16	16	24	24	24	
	6.55 (2.37)	6.17 (2.55)	-0.38 (2.33)	5.52 (1.86)	3.80 (2.29)	-1.72 (2.51)	0.015
No Fludrocortisone Use, n	63	63	63	56	57	56	
	4.56 (2.29)	3.51 (2.35)	-1.06 (1.53)	4.87 (1.93)	3.07 (2.14)	-1.89 (1.89)	0.012
Enzymatic Degradation Agent Use, n	11	11	11	21	21	21	
	5.67 (2.66)	4.58 (2.79)	-1.09 (1.74)	5.30 (1.84)	4.30 (2.16)	-1.00 (2.14)	0.972
No Enzymatic Degradation Agent Use, n	68	68	68	59	60	59	
	4.85 (2.39)	3.96 (2.59)	-0.89 (1.74)	4.98 (1.96)	2.93 (2.12)	-2.14 (1.99)	<0.001
Dopaminergic Use, n	35	35	35	36	37	36	
	5.21 (2.25)	4.15 (2.32)	-1.07 (1.46)	5.48 (1.74)	4.12 (2.16)	-1.48 (2.10)	0.425
No Dopaminergic Use, n	44	44	44	44	44	44	
	4.77 (2.57)	3.97 (2.84)	-0.80 (1.92)	4.73 (2.02)	2.59 (2.01)	-2.14 (2.03)	0.001
Baseline OH Severity							
Clinician-rated CGI-S							
Normal-Borderline OH (CGI-S 1-2), n	1	1	1	0	0	0	
	8.25	7.46	-0.79				--
Mild-Moderate OH (CGI-S 3-4), n	47	47	47	41	41	41	
	4.04 (2.32)	3.42 (2.31)	-0.62 (1.36)	4.54 (1.96)	2.73 (2.20)	-1.81 (1.99)	0.003
Marked OH-Most Ill with OH (CGI-S 5-7), n	31	31	31	39	40	39	
	6.27 (1.90)	4.89 (2.78)	-1.37 (2.14)	5.62 (1.74)	3.86 (2.07)	-1.88 (2.19)	0.152

Subgroup	Placebo, Mean (SD)			Droxidopa, Mean (SD)			ANCOVA[3]
	Randomization	End of Study	Δ	Randomization	End of Study	Δ	
Dose Group							
100 mg TID, n	5	5	5	5	5	5	
	3.88 (2.11)	2.56 (2.47)	-1.33 (2.73)	5.15 (2.19)	3.88 (2.53)	-1.28 (1.14)	0.773
200 mg TID, n	7	7	7	9	9	9	
	3.45 (3.21)	3.53 (2.93)	0.08 (2.01)	4.06 (2.14)	3.51 (2.38)	-0.55 (2.38)	0.710
300 mg TID, n	24	24	24	11	11	11	
	4.74 (2.09)	3.58 (2.16)	-1.17 (1.75)	4.10 (1.85)	3.70 (2.50)	-0.41 (1.93)	0.368
400 mg TID, n	19	19	19	16	16	16	
	5.46 (2.50)	4.94 (3.12)	-0.52 (1.79)	6.00 (1.58)	2.68 (1.80)	-3.31 (1.83)	<0.001
500 mg TID, n	9	9	9	10	10	10	
	4.50 (2.53)	3.56 (2.38)	-0.95 (1.22)	4.72 (1.87)	3.08 (2.67)	-1.65 (2.48)	0.489
600 mg TID, n	15	15	15	29	30	29	
	6.03 (2.20)	4.69 (2.46)	-1.34 (1.30)	5.33 (1.86)	3.36 (2.12)	-2.14 (1.58)	0.050

Source: 301 Study Report, section 11.5

5.3.2 Study 302

Title of the study: A Multi-Center, Double-Blind, Randomized, Placebo-Controlled, Parallel-Group, Withdrawal-Design Study to Assess the Clinical Effect of Droxidopa in Subjects with Primary Autonomic Failure, Dopamine Beta Hydroxylase Deficiency, or Non-Diabetic Neuropathy and Symptomatic Neurogenic Orthostatic Hypotension

Study center(s): 71 centers in 6 countries

Study Period:

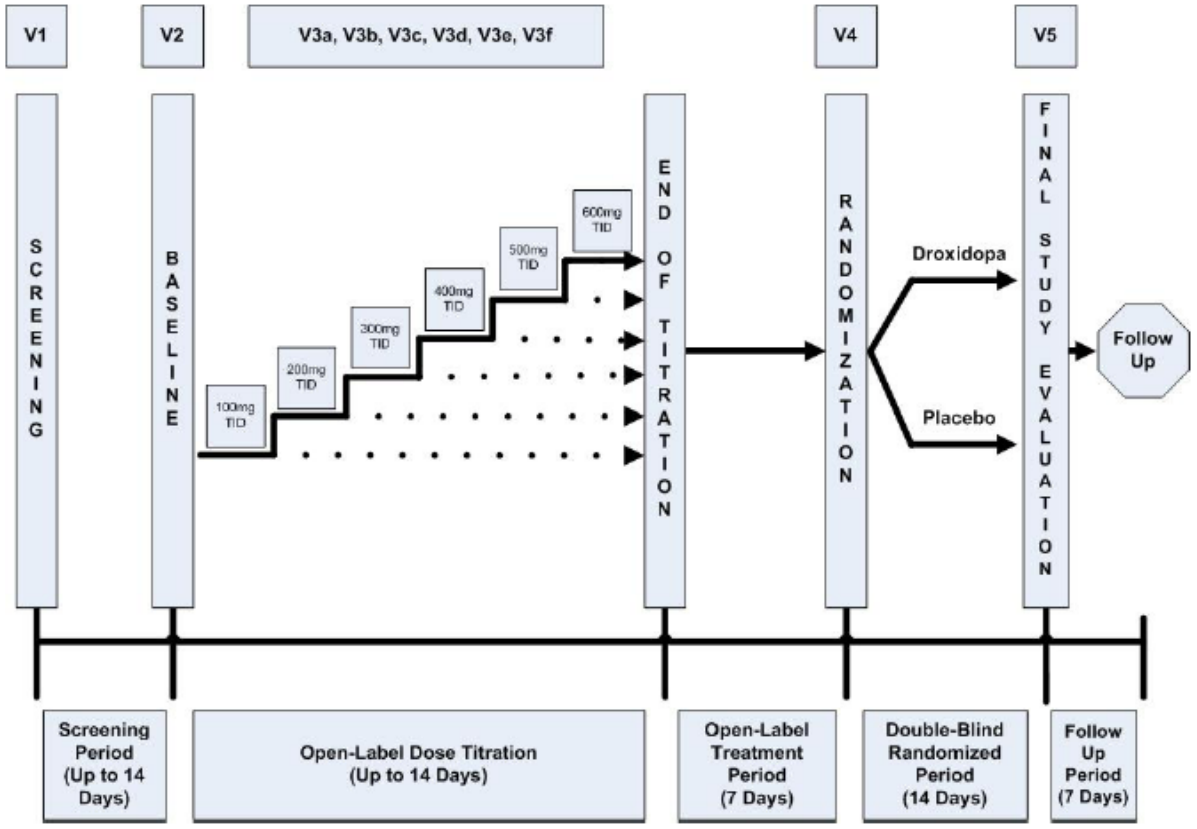
Study Initiation Date: February 1, 2008 (first patient enrolled)
Study Resized: February 26, 2009.
Study Completion Date: August 10, 2009

Methodology:

Like Study 301**,** Study 302 was a Phase 3, multi-center, multi-national, randomized-withdrawal, placebo-controlled, parallel-group, double-blind study with an initial open-label dose titration induction phase (up to 14 days). In Study 302, the induction phase was followed by 7 days of open-label treatment (instead of the washout in Study 301), followed by a 14-day randomized withdrawal period and a final clinic visit. There was also a telephone visit 7 days later. See Figure 16 for a schematic diagram of the study design.

The study was designed to evaluate the effect of a randomized withdrawal (to placebo) on the clinical effect (efficacy and safety) of droxidopa in similar patients to those enrolled in Study 301 [(symptomatic NOH associated with primary autonomic failure (PD, MSA and PAF), Dopamine Beta Hydroxylase (DBH) Deficiency, or Non-Diabetic Autonomic Neuropathy (NDAN)]. Patients had baseline measurements after it was established that hey had orthostatic hypotension defined as either a 20 mmHg systolic or 10 mmHg diastolic decrease in BP, within 3 minutes after standing.

Figure 16: Study Design for Study 302



Source: Study 302 Study Report, Section 9.1.1 p. 20

The enrollment criteria were the same as in Study 301. The same criteria were followed as in Study 301 to decide upon droxidopa dose and whether a patient would be considered to be a responder. The same doses and dosing schedule for droxidopa were employed.

Additionally, the same questionnaires were used as Study 301 for efficacy evaluations.

Efficacy Evaluation:

The primary efficacy endpoint was the mean change from Randomization (Visit 4) to the End of Study Visit (Visit 5) in the OHSA Item 1 (dizziness, lightheadedness, feeling faint or feeling like you might black out) score. Patients were instructed to rate these symptoms as experienced on average over the past week.

The prespecified statistical test to compare droxidopa and placebo groups for the primary efficacy endpoint was the Wilcoxon rank-sum test using the full analysis set (FAS) with missing data imputed using the Last Observation Carried Forward (LOCF) method. Since there was only one assessment of the OHSA following randomization,

missing values at day 14 were assumed to have a change from randomization equal to 0.

The FAS consisted of all randomized patients who received at least one dose of double-blind medication (a modified intent-to-treat [mITT] population).

The secondary efficacy endpoints for this study had no prespecified hierarchy stated in the SAP. They were:
1) SBP and DBP measurements 3 minutes post standing;

2 Global assessment evaluations using the clinician-recorded and patient-recorded CGIS and CGI-I scales;

3) Symptom and activity measurements using the scores of OHSA and OHDAS

Protocol Changes:

On February 26, 2009, Study 302 was resized from 118 to 82 total patients. The initial sample size calculation for Study 302 estimated a standard deviation of 3.0 for the primary endpoint (i.e., OHSA Item 1). Subsequent data from other studies enabled a re-evaluation of the standard deviation, which resulted in lowering the estimate from 3.0 to 2.5. Using an overall 0.05 two-sided significance level, a new sample size of 41 evaluable patients in each randomized treatment group in a 1:1 ratio (i.e., 82 patients in total) was determined to have 80% power to detect a difference of 1.6 points between placebo- and droxidopa-treated patients with respect to change from Randomization to End of Study in OHSA Item 1.

Other amendments included an interim analysis which was changed to an “optional” unblinded analysis to look for a statistically significant difference between the treatment groups. Most amendments were to protect the safety or increase the comfort of the individuals enrolled in the trial or were administrative. An extension phase was also added.

Safety and tolerability Assessments:

The safety data collected in Study 302 were: (1) AEs; (2) physical examinations; (3) vital signs (BP, HR); (4) ECGs; and (5) blood and urine laboratory safety tests.

> **REVIEWER'S COMMENT(S): The randomized withdrawal design of Study 302 is helpful in understanding if there is maintenance of effect of a drug. If one counts the up to 14 day induction/titration phase (where albeit, the patients mostly received lower doses), the patients who were randomized to the droxidopa group actually had a total of up to 35 days of uninterrupted treatment before the final efficacy testing was done. In**

principle, this is a good design and might have been helpful in establishing some durability of effect, at least more so than Study 301 which only tested the effects of droxidopa after one week.

Results:

Demographics:

As shown in Table 12, demographic characteristics (patients that received at least one dose of drug) were similar between the placebo and droxidopa treatment groups. The mean ages were 66.6 and 63.1 years for patients in the placebo and droxidopa groups, respectively. There were more males (62.7% and 60.0% for the placebo and droxidopa groups, respectively) than females in the study. The patients were predominantly Caucasian in both groups. The droxidopa group was mostly composed of patients with a primary diagnosis of PD (42.0%), MSA (34.0%), or PAF (16.0%); similar proportions were observed in the placebo group (45.1%, 25.5% and 19.6%, respectively). None of the patients in the droxidopa group had DBH deficiency. As shown in Table 13, the Baseline performance on Item 1 of the OHSA (dizziness, the primary efficacy endpoint) and the Baseline mean SBP values post-standing at 3 minutes were similar between the placebo and droxidopa treatment groups (FAS). At Visit 2, prior to titration, the mean Baseline OHSA Item 1 scores were 6.3 and 6.6 units for the placebo and droxidopa groups, respectively, and the mean SBP values post-standing at 3 minutes were 88.0 and 87.0 mmHg for the placebo and droxidopa groups, respectively. Of note, the Baseline OHQ composite scores were 6.0 and 6.2 units for the placebo and droxidopa groups, respectively.

Table 12: Demographics and Patient Baseline characteristics for Study 302

		Randomized Controlled Treatment	
	Not Randomized[2] (N=80)	**Placebo** (N=51)	**Droxidopa** (N=50)
Primary Clinical Diagnosis [n (%)]			
PD	38 (47.5)	23 (45.1)	21 (42.0)
MSA	21 (26.3)	13 (25.5)	17 (34.0)
PAF	18 (22.5)	10 (19.6)	8 (16.0)
DBH Deficiency	0	1 (2.0)	0
Non-Diabetic Autonomic Neuropathy	2 (2.5)	3 (5.9)	2 (4.0)
Other Diagnosis	1 (1.3)	1 (2.0)	2 (4.0)
Age (Years) at Screening			
Mean ± SD	69.5 (9.74)	66.6 (11.25)	63.1 (13.76)
Min, Max	37, 86	40, 88	24, 88
Gender [n (%)]			
Male	45 (56.3)	32 (62.7)	30 (60.0)
Female	35 (43.8)	19 (37.3)	20 (40.0)
Region [n (%)]			
US	53 (66.3)	32 (62.7)	25 (50.0)
Non-US	27 (33.8)	19 (37.3)	25 (50.0)
Race [n (%)]			
White	79 (98.8)	48 (94.1)	49 (98.0)
Asian	0	1 (2.0)	1 (2.0)
American Indian/Alaskan Native	0	1 (2.0)	0
Hispanic/Latino	1 (1.3)	1 (2.0)	0
Weight (kg)			
N	79	50	50
Mean (SD)	75.71 (17.86)	73.02 (14.24)	76.66 (20.29)
Min, Max	45.4, 177.8	38.6, 99.0	47.0, 183.0
Baseline OHQ Composite Score			
n	--	49	50
Mean (SD)	--	6.04 (2.22)	6.22 (1.86)
Min, Max	--	0.9, 9.5	2.1, 9.6

DBH=Dopamine beta hydroxylase; MSA=Multiple System Atrophy; OHQ=Orthostatic Hypotension Questionnaire; PAF= Pure Autonomic Failure; PD=Parkinson's disease; Max=Maximum; Min=Minimum; SD=Standard deviation; US=United States.
1 Data presented for the Randomized Treatment groups represent the Full Analysis Set. Data presented for the patients who were not randomized represent the Safety Set; the patients in the titration phase of the study who were not randomized are not included in the Full Analysis Set
2 Patients who were titrated but not randomized were included only in the Not Randomized column.
Source: Study 302 Study Report, Section 11.2, p. 63

Table 13: Baseline Scores of Disease Severity and SBP upon Standing + 3 Minutes (mmHg)

Parameter	Placebo (N=51)	Droxidopa (N=50)
Baseline OHSA Item 1 Score		
n	51	50
Mean (SD)	6.3 (2.27)	6.6 (2.01)
Min, Max	2, 10	3, 10
Baseline SBP upon Standing +3 Minutes (mmHg)		
n	50	50
Mean (SD)	88.0 (19.04)	87.0 (17.60)
Min, Max	50, 130	37, 116

OHSA=Orthostatic Hypotension Symptom Assessment; Max=Maximum; Min=Minimum; SBP=Systolic blood pressure; SD=Standard deviation.

Source: Study 302 Study Report, Section 11.2 , p. 64

Disposition

Of the 181 patients treated, 101 were randomized (and became the FAS): 51 in the placebo group and 50 in the droxidopa group. Of those, 43 patients in the placebo group and 44 patients in the droxidopa group finished the study per-protocol according to the sites. Treatment failure was the main reason why patients did not make it to the double blind phase (55/80), followed by adverse events (13/80). One patient who was in the placebo group did not complete the double blind phase per protocol because of treatment failure and only two patients in the placebo group did not complete the double blind (DB) phase per protocol for adverse events. The most common reasons for those randomized to droxidopa not finishing the DB phase per protocol were protocol violations.

Compliance

Mean compliance (calculated as [amount of drug taken/amount that should have been taken]*100) was 118.2% and 86.2% in the placebo and droxidopa groups, respectively.

REVIEWER'S COMMENT(S): The lower compliance in the droxidopa group works against finding a treatment effect.

Concomitant Medications

The majority (>95%) of patients in the study took concomitant medications. DOPA and DOPA derivatives were the most common concomitant medications by ATC class and their use was comparable between placebo-treated (56.9%) and droxidopa-treated patients (54.0%). However, mineralocorticoids were used by more the droxidopa treatment group (32.0% vs. 25.5%).

Efficacy Analysis

The Statistical plan was followed according to the final submitted plan.

Primary Endpoint

As shown in Table 14, Study 302 failed on its primary endpoint. Since this is a randomized withdrawal design, the desired results were that the placebo group would worsen (reflected by OHSA Item 1 increasing) because they were being taken off of drug, and the droxidopa treatment group would stay the same or improve if the drug effect improves over time (reflected by OHSA Item 1 decreasing).

The results were not favorable: both groups worsened considerably. Numerically, the droxidopa treatment group did not worsen as much as the placebo treatment group on the OHSA Item 1 (1.3 worsening for the droxidopa treatment group vs. 1.9 worsening for the placebo group). It is notable that even with a +1.9 worsening for the placebo group, the final score was 4.0, still much better than the baseline score of 6.3. The change in the droxidopa group was 1.3, resulting in a final score of 3.5; also much better than the baseline score of 6.6.

> **REVIEWER'S COMMENT(S): Why did the patients on droxidopa get 1.3 points worse despite no change in therapy? And why did the placebo treated patients not worsen back to their baseline? Clearly these results draw the efficacy of droxidopa into question. It is possible that the patients have improvements in their baseline scores because they are enrolled in a clinical trial and that after randomization, both groups worsen because the "placebo effect" of being in a trial begins to wear off. Another possible explanation for the negative findings is that the drug does have efficacy but that it diminishes over time. Yet another interesting possibility is that droxidopa has a carry-over effect that prevented the placebo treated patients from returning fully to their baseline, but this is purely speculative.**

Table 14: Summary of OHSA Item 1 Score[1] (Full Analysis Set with LOCF[2])

	Placebo (N=51)	Droxidopa (N=50)	p-value[3]
Randomization (Visit 4)			
N	51	50	
Mean (SD)	2.1 (2.51)	2.1 (2.19)	
Min, Max	0, 8	0, 8	
End of Study (Visit 5)			
N	51	50	
Mean (SD)	4.0 (3.58)	3.5 (3.17)	
Min, Max	0, 10	0, 10	
Change from Randomization to End of Study			
N	51	50	0.509
Mean (SD)	1.9 (3.16)	1.3 (2.75)	
Min, Max	-4, 9	-6, 9	

LOCF=Last observation carried forward; OHSA=Orthostatic Hypotension Symptom Assessment; Max=Maximum; Min=Minimum; SD=Standard deviation.
1 The OHSA composite score is the average of Items 1-6 with a score of 1 or more at the Baseline Visit.
2 Missing data were imputed using the LOCF method.
3 The change from Randomization was evaluated using the Wilcoxon rank-sum test.
Source: Table 5.1.1.

Source: Study 302 Study Report, Section 11.4.1.1 , p. 66

Secondary Endpoints/ exploratory analyses

Study 302 lost on its first secondary endpoint (standing systolic BP at 3 minutes) as shown in Table 15. The patients initially had a substantial rise in standing systolic blood pressure during the titration phase. This initial rise would be a surprising finding with a drug that had no effect on SBP. Paradoxically, the standing SBP diminished after randomization in both treatment groups [even more so in the droxidopa treatment group than the placebo treatment group (-7.6 compared to -5.2, p=0.680)]. This does cause one to wonder if the effect of droxidopa might diminish over time.

REVIEWER'S COMMENT(S): Droxidopa passes through the blood brain barrier. By binding to alpha adrenergic receptors it may have a central depressant effect on SBP. Alpha adrenergic receptors in the brain close a negative feedback loop that begins with descending sympathetic nerves from the brain that control the production of catecholamines in the adrenal medulla. By fooling the brain into believing that catecholamine levels are higher than they really are, droxidopa, by its intracerebral conversion to NE, might cause the brain to reduce its signals to the adrenal medulla, which in turn might lower catecholamine production and blood levels. It is possible that there is down-regulation of catecholamine production in

droxidopa-treated patients which might counterbalance the peripheral catecholamine raising effect of droxidopa. Another possibility is that there is down-regulation of peripheral NE receptors that could explain the decrease in SBP seen in patients who stay on droxidopa.

Table 15: Summary of Systolic Blood Pressure (mmHg) During Orthostatic Standing Test (FAS)

	Placebo N=51			Droxidopa N=50		
SBP upon Standing +3 Minutes (mmHg)	**Result**	**Change from Baseline**	**Change from Randomization**	**Result**	**Change from Baseline**	**Change from Randomization**
Baseline (n)	50			50		
Mean (SD)	88.0 (19.04)	--	--	87.0 (17.60)	---	--
Min, Max	50, 130			37, 116		
End of Titration (n)	50	49		49	49	
Mean (SD)	112.4 (22.78)	25.5 (15.98)	--	109.1 (19.39)	22.6 (15.80)	--
Min, Max	66, 170	7, 77		65, 155	3, 70	
Randomization (n)	49	48		50	50	
Mean (SD)	101.1 (24.24)	12.0 (20.83)	--	106.3 (22.28)	19.4 (16.17)	--
Min, Max	58, 156	-22, 58		52, 153	-7, 70	
End of Study (n)	50	49	48	50	50	50
Mean (SD)	96.0 (22.49)	8.2 (22.65)	-5.2 (26.83)	98.8 (27.07)	11.8 (23.43)	-7.6 (19.71)
Min, Max	53, 157	-38, 72	-56, 75	48, 154	-30, 84	-63, 56
p-value [1]					0.488	0.680

Max=Maximum; Min=Minimum; SBP=Systolic blood pressure; SD=Standard deviation.
1 The differences between placebo and droxidopa with respect to changes from Baseline and Randomization are evaluated using Wilcoxon rank-sum tests.

The OHQ is divided into the OHSA and the OHDAS which have 6 and 4 items, respectively. As shown in Table 16 and Figure 17, none of the OHSA Items 2-6 showed a difference between placebo and droxidopa. The OHDAS items of the OHQ showed favorable results. It must be kept in mind that the OHDAS is not a symptom questionnaire but shows impacts of symptoms on activities. It is odd that there would be an improvement on an impact of symptoms questionnaire and not on the symptoms themselves. This result is confusing and causes one to question the validity of the OHDAS.

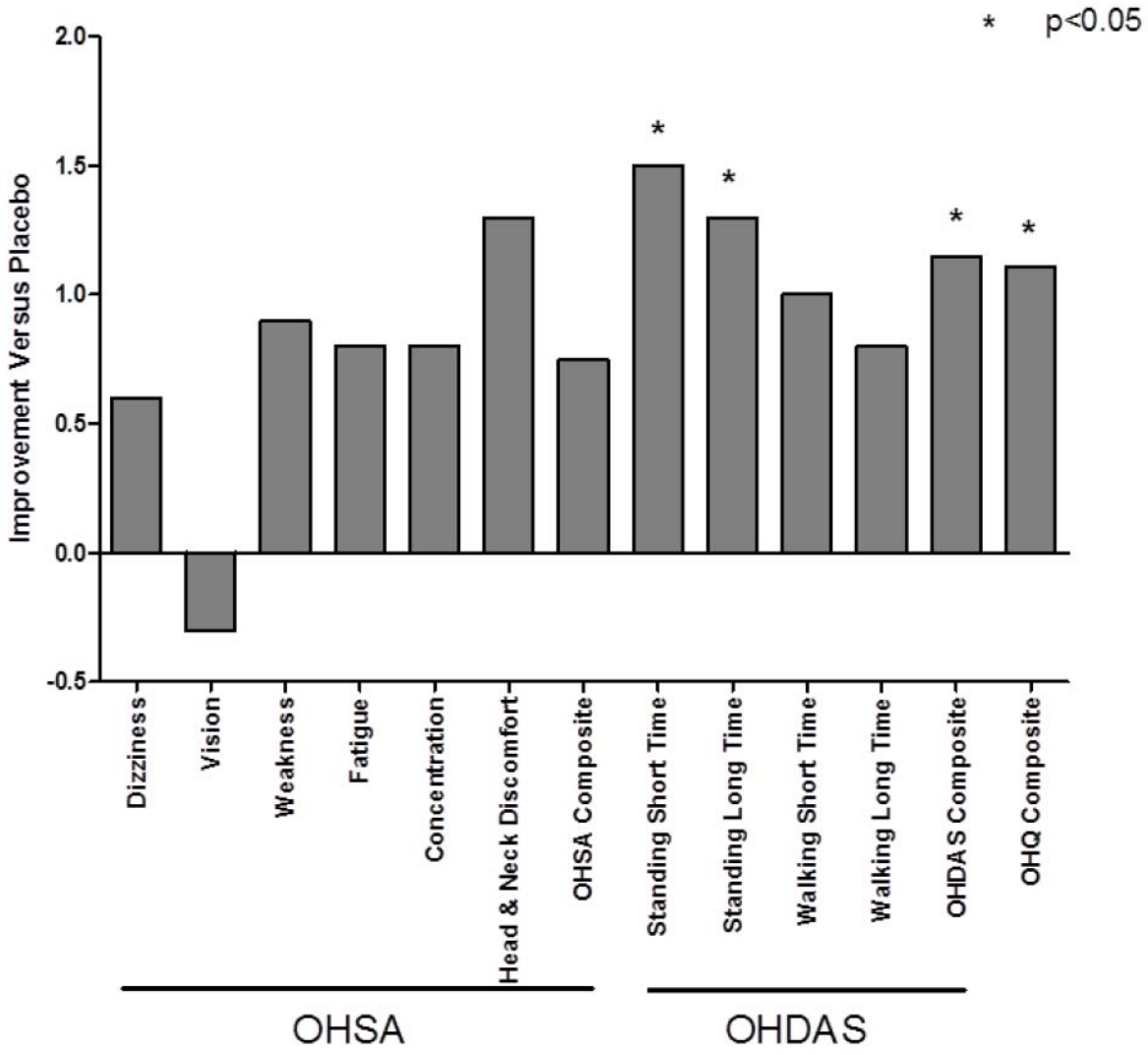
Table 16: Summary of the OHSA Item 2 – 6 Scores and Composite Scores (Full Analysis Set with LOCF [1])

OHSA Item Symptom	Placebo, Mean (SD) N=51			Droxidopa, Mean (SD) N=50			p-value [2]
	Randomization	End of Study	Δ	Randomization	End of Study	Δ	
Item #2 (n)	51	51	51	50	50	50	
Vision	1.4 (2.10)	2.2 (2.91)	0.8 (2.24)	1.6 (2.00)	2.7 (2.82)	1.1 (2.79)	0.833
Item #3 (n)	51	51	51	50	50	50	
Weakness	2.5 (2.74)	3.7 (3.28)	1.2 (2.70)	2.7 (2.48)	3.0 (3.06)	0.3 (2.88)	0.214
Item #4 (n)	51	51	51	50	50	50	
Fatigue	2.5 (2.52)	3.9 (3.24)	1.5 (2.72)	2.7 (2.69)	3.4 (2.74)	0.7 (2.61)	0.233
Item #5 (n)	51	51	51	50	50	50	
Concentration	1.6 (2.04)	2.5 (2.76)	0.9 (2.67)	2.3 (2.60)	2.4 (2.59)	0.1 (2.74)	0.113
Item #6 (n)	51	51	51	50	50	50	
Head/Neck Discomfort	2.0 (2.60)	3.2 (3.75)	1.2 (3.19)	2.2 (2.41)	2.1 (2.60)	-0.1 (2.45)	0.097
OHSA Composite (n)	51	51	51	50	50	50	
	2.11 (1.94)	3.46 (2.93)	1.35 (2.53)	2.44 (1.88)	3.04 (2.43)	0.6 (2.27)	0.160
OHSA Composite (n)	50	50	50	50	50	50	
Items 2-6	2.15 (1.95)	3.22 (2.80)	1.07 (2.25)	2.52 (1.99)	2.96 (2.39)	0.44 (2.29)	0.200

Δ=Change; LOCF=Last observation carried forward; OHSA=Orthostatic Hypotension Symptoms Assessment; SD=Standard deviation.
1 Missing data were imputed using the LOCF method.
2 The change from Randomization was evaluated using the Wilcoxon rank-sum test.

Source: Study 302 Study Report, Section 4.2.7.2., p. 70

Figure 17: Improvements in OHQ Individual Items and Composite Scores



OHDAS=Orthostatic Hypotension Daily Activity Scale; OHQ=Orthostatic Hypotension Questionnaire; OHSA=Orthostatic Hypotension Symptom Assessment.
Note: The differences between placebo and droxidopa with respect to changes from Randomization were evaluated using a Wilcoxon rank-sum test.

Source: Study 302 Study Report, Figure 11-1, section 11.4.6, p. 86

The OHQ analysis was not prespecified as an efficacy endpoint in the statistical analysis plan. However, it was analyzed to see if a difference between the placebo and droxidopa treatment groups could be identified. The results of this exploratory analysis of the OHQ were positive with droxidopa showing superiority to placebo. The results are shown in Table 17.

REVIEWER'S COMMENT(S): Absence of a worsening in OHQ scores in the droxidopa treatment group could be interpreted as providing evidence that the effects of droxidopa are stable over at least 3 weeks of treatment. This was, however, an exploratory analysis and one needs to be careful about overinterpreting the results.

Table 17: Summary of OHQ Composite Score (Study 302 Full Analysis Set with LOCF)

	Placebo N=51			Droxidopa N=50			p-value[1]
	Randomization	End of Study	Δ	Randomization	End of Study	Δ	
N	50	51	50	50	50	50	0.042
Mean (SD)	2.83 (2.22)	3.90 (3.00)	1.14 (2.40)	3.03 (2.09)	3.21 (2.50)	0.18 (2.11)	
Min, Max	0, 8.1	0, 9.4	-4.2, 7.8	0, 7.7	0, 9.5	-5.3, 7.7	

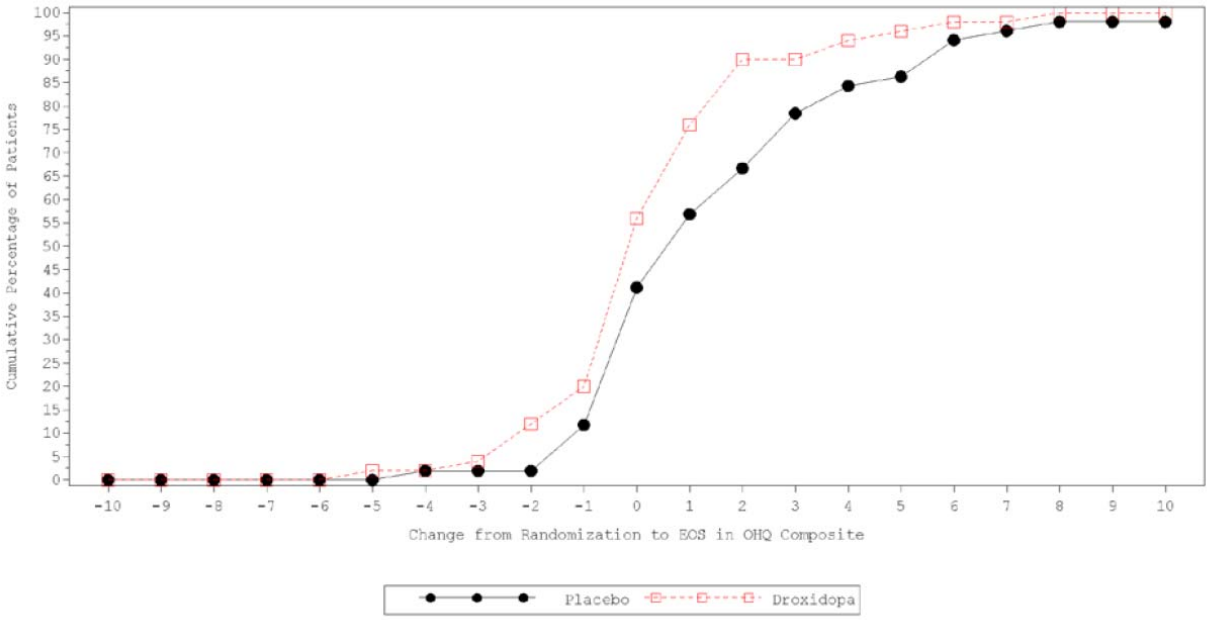
ANCOVA=Analysis of covariance; Δ=Change; OHQ=Orthostatic Hypotension Questionnaire; Max=Maximum; Min=Minimum; SD=Standard deviation.

1 The p-value from the ANCOVA model included a factor for randomized treatment along with the OHQ composite value at Randomization as a covariate.

Source: Integrated Summary of Efficacy, Section 4.2.7.1., p. 84

The cumulative distribution of results of the OHQ (Figure 18) showed that most patients in the droxidopa treatment group (~60%) had score changes of 0 or less (no change or improvement) whereas only ~40% of the patients on placebo had changes of 0 or less after the two-week randomized withdrawal period. Another observation is that there were more patients on placebo who had marked worsening of their composite scores.

Figure 18: Cumulative distribution curve of OHQ score composite (FAS with LOCF for missing data)



Source: Clinical Overview

There were two other positive exploratory findings in study 302: 1) there was a nominally statistically significant difference favoring droxidopa in the patient-rated CGI-S score (p=0.008) and 2) there was a strong trend favoring droxidopa in the clinician-rated CGI-S score (p=0.052). These more general measures of clinical status are supportive findings of efficacy.

While there were few patients in each of the subgroups by underlying disease, it is notable that the patients with Pure Autonomic Failure did strikingly better on droxidopa than placebo on the OHQ (Table 18).

Table 18: Summary of OHQ Composite Score by Primary Diagnosis (Full Analysis Set)

Subgroup	Placebo, Mean (SD)					Droxidopa, Mean (SD)					Δ CFR p-value[2]	Δ CFB p-value[3]
	Baseline	Random-ization	End of Study	CFR	CFB	Baseline	Random-ization	End of Study	CFR	CFB		
PD, n	53	52	53	52	53	56	56	56	56	56		
	5.62	3.82	3.57	-0.18	-2.05	6.08	4.28	3.26	-1.02	-2.82	0.085	0.094
	(2.04)	(2.59)	(2.51)	(2.14)	(2.34)	(1.58)	(2.04)	(2.12)	(2.16)	(2.43)		
MSA, n	22	22	22	22	22	31	28	31	28	31		
	6.72	4.91	5.05	0.14	-1.67	6.52	4.46	3.58	-1.02	-2.94	0.018	0.036
	(1.79)	(2.54)	(2.86)	(2.39)	(2.67)	(1.59)	(2.42)	(2.23)	(1.81)	(2.16)		
PAF, n	38	38	38	38	38	34	34	34	34	34		
	5.65	4.36	4.10	-0.26	-1.55	5.79	4.29	2.75	-1.54	-3.04	0.022	<0.001
	(2.17)	(2.49)	(2.71)	(2.35)	(2.16)	(2.04)	(2.41)	(2.67)	(2.90)	(2.10)		
NDAN, n	9	9	9	9	9	4	4	4	4	4		
	6.07	4.22	4.06	-0.16	-2.01	6.28	4.59	2.77	-1.82	-3.51	0.331	0.440
	(1.83)	(2.76)	(3.49)	(2.49)	(2.59)	(1.28)	(2.83)	(1.60)	(2.67)	(2.35)		
Other, n	5	5	5	5	5	6	5	6	5	6		
	4.29	2.03	2.78	0.76	-1.51	6.38	3.58	4.99	0.75	-1.40	0.931	0.715
	(1.77)	(2.05)	(3.37)	(2.77)	(2.64)	(1.84)	(2.07)	(2.92)	(1.10)	(1.66)		

CFR= Change from Randomization, CFB= Change from Baseline
Source: Integrated Summary of Efficacy, Section 5.2.1.1., p. 104

5.3.3 Study 303

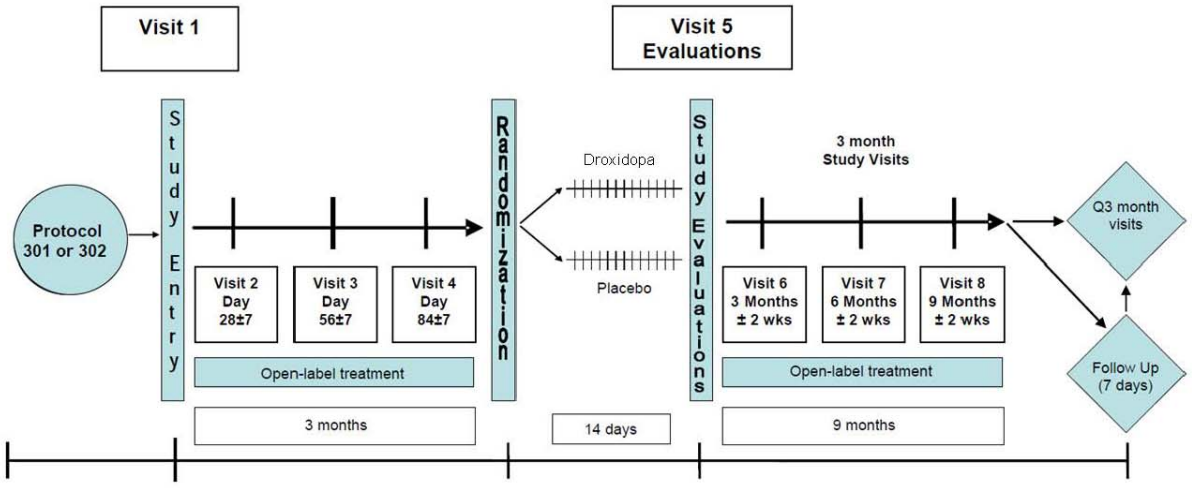
Title of the study: A Multicenter, Open-Label Study with a Two-Week Randomized, Placebo-Controlled Withdrawal Period to Assess the Long-term Safety and Clinical Benefit of Droxidopa in Subjects With Primary Autonomic Failure, Dopamine Beta-Hydroxylase Deficiency, or Non-diabetic Neuropathy and Symptomatic Neurogenic Orthostatic Hypotension

Study Period:
Study Initiation Date: April 4, 2008 (First Patient First Visit)
Study Completion Date: October 22, 2010 (Last Patient Last Visit)

Methodology: Study 303 was a Phase 3, multi-center, multi-national outpatient study with an initial 3 month open-label treatment period followed by a 2-week double-blind, placebo-controlled, randomized-withdrawal period, followed by open-label treatment for the remaining study duration. After the 2-week randomized withdrawal, patients entered a 9-month OL study. All of the patients in 303 had been enrolled in studies 301 or 302. Any patient with a symptomatic response to droxidopa during the OL titration phase of Studies 301 and 302 could be enrolled in Study 303 even if they did not have changes in their blood pressure during treatment.

See Figure 19 for a schematic depiction of the study design.

Figure 19: Study Design for Study 303



Source: Study 303 Study Report, Section 9.1.1 p. 21

In the initial 3-month open-label treatment period, patients returned to the clinic every 4 weeks for study evaluations (Day 28±7 days, Day 56±7 days, and Day 84±7 days). At each visit, patients were required to undergo an orthostatic standing test 3 hours after their morning dose of study treatment and to complete efficacy and safety evaluations. At any time during the study, patients who prematurely withdrew from the study were asked to visit the study center for a final assessment and the procedures described for Day 84 (Visit 4) were conducted.

At the Day 84 visit, patients were randomly assigned to continued treatment on their individualized dose of droxidopa, or to matching placebo, for a 2-week treatment period. Patients returned to the clinic for efficacy and safety evaluations at the end of the 2-week period. At the conclusion of the 2-week randomized-withdrawal period, all patients who had continued to benefit from treatment with open-label droxidopa were entered into a 9-month open-label follow-up period.

Primary Objective: to examine the safety and efficacy of long-term administration of droxidopa; specifically, whether the positive patient-reported outcomes and BP findings observed with the short-term administration (1 or 2 weeks) were durable over an extended treatment period in these chronically ill patients. Despite this objective, the sponsor claims that the study was not designed to be adequately powered to demonstrate a statistically significant treatment benefit in the randomized-withdrawal portion of the study. Based on the results from Study 302, a difference in the mean OHQ composite score of 1.11 and a standard deviation of 2.39, study 303 had only 50% power to detect a difference between treatment arms with 75 randomized patients.

Criteria for evaluation:
The primary efficacy endpoint was the mean change from Randomization (Visit 4) to the end of the 2-week randomized treatment period in OHQ scores.

The secondary efficacy endpoints for this study were individual items of the OHSA and the OHSA composite, individual items of the OHDAS and the OHDAS composite score, global clinical assessments (CGI-I and CGI-S) and SBP, DBP and HR values during the orthostatic standing test.

All secondary efficacy endpoints were evaluated using the FAS with missing data imputed using LOCF.

Protocol Changes
Dose titration was allowed for the purpose of reducing side effects.

Safety and tolerability assessments included:

The safety data collected in Study 303 were: (1) AEs; (2) physical examinations; (3) vital signs (BP, HR); (4) ECGs; and (5) blood and urine laboratory safety tests.

REVIEWER'S COMMENT(S):
The randomized withdrawal design of Study 303 after 3 months of droxidopa is the only trial that allowed for the evaluation of maintenance of efficacy after a considerably long treatment period treatment (3 months). The Agency told the sponsor in the pre-IND meeting of 5/01/2007 that it was important to test the drug over an extended period for the assessment of durability of effect. It is not clear why the sponsor did not power Study 303 appropriately.

Results:
Of the 103 patients enrolled in Study 303, 27 did not enroll in the double-blind phase. The others were randomized 1:1 to either drug or placebo for a two week period (37 randomized to placebo and 38 randomized to droxidopa). See Table 19 for a description of the analysis populations.

Analysis Populations

Table 19: Analysis Populations

	Three-Month Open-Label Droxidopa[1] (N=28)	Double-Blind Phase		Total (N=103)
		Placebo (N=37)	Droxidopa (N=38)	
Analysis Populations				
Safety Set[2], n (%)	27 (96.4)	37 (100.0)	38 (100.0)	102 (99.0)
Full Analysis Set[3], n (%)	N/A	37 (100.0)	38 (100.0)	75 (72.8)
Per Protocol Set[4], n (%)	N/A	29 (78.4)	35 (92.1)	64 (62.1)

1 Patients received 3 months of open-label droxidopa prior to the randomized-withdrawal period. Patients who were not randomized were included only in the Three-Month Open-Label Droxidopa column.
2 All patients who received at least one dose of study drug were included in the Safety Set. This includes patients who were not randomized but received study drug during the open-label treatment phase. Patients were included in the analysis according to the treatment received.
3 The Full Analysis Set consisted of all randomized patients following the principle of intention to treat (ITT). Patients were included in the analysis according to the treatment to which they were randomized. Patients who withdrew from the study prior to Randomization were excluded from the Full Analysis Set.
4 The Per Protocol Set is the Full Analysis Set excluding patients and/or data with violations/deviations deemed sufficiently serious to warrant exclusion from the analysis.
Note: Percentages for the analysis populations were based on the number of patients randomized or treated in each group.

Source: Study report for Study 303, table 11-1, section 11.1, p. 55

Disposition

Of the 102 patients who received at least one dose of droxidopa, 75 were randomized. 79 completed the OL phase. 69 completed the double-blind phase. 54 patients completed per protocol. The disposition data is presented in Table 20.

Table 20: Disposition of Patients in Study 303

Total patients studied	102
Patients randomized	75
Patients completed OL phase	79
Patients completed DB phase	69
Patients completed per protocol	54
Reason for not Completing Study per protocol	
Treatment failure	4(8.2)
Adverse event	20 (40.8)
Lack of efficacy	3 (6.1)
Protocol violation	2(4.1)
Lost to follow up	1 (2.0)
Withdrew consent	16 (32.7)
Investigator decision	1 (2.0)
Other	
Patient didn't meet inclusion criteria	1 (2.0)
Possible untoward effect of droxidopa on coagulation (after SAE), decision of PI and Medical Advisor	1 (2.0)

Primary Endpoint

As shown in Table 21, the treatment groups did not differ greatly from each other on the OHQ score at the end of the two week double-blind randomized withdrawal phase indicating a lack of sustained effect on symptoms of OH or a carry-over effect of droxidopa. The difference from beginning of randomization was an increase (worsening) of 0.90 points for the placebo group and an increase (worsening) of 0.57 for the droxidopa treatment group. The trend was that the droxidopa group did not worsen as much as the placebo group. Nevertheless, there was no statistically significant difference between treatment groups in change in OHQ from beginning of randomization to the end of study (p=0.44). A similar trend was seen with the OHSA 1 as shown in Table 22.

Table 21: Summary of OHQ Composite Score[1] for Study 303 (FAS with LOCF[2])

	Placebo N=37			Droxidopa N=38		
OHQ Composite Score	**Result**	**Change from Baseline**	**Change from Randomization**	**Result**	**Change from Baseline**	**Change from Randomization**
Baseline[3] (n)	37			37		
Mean (SD)	6.27 (1.948)	--	--	6.38 (1.848)	--	--
Min, Max	2.1, 9.2			3.0, 9.6		
Open-Label Month 1 (n)	37	37		37	37	
Mean (SD)	3.04 (2.665)	-3.23 (2.433)	--	3.30 (2.366)	-3.08 (2.358)	--
Min, Max	0.0, 8.8	-8.7, 0.8		0.0, 9.0	-8.1, 2.4	
Open-Label Month 2 (n)	37	37		37	37	
Mean (SD)	3.03 (2.479)	-3.24 (2.362)	--	3.44 (2.144)	-2.94 (2.073)	--
Min, Max	0.0, 8.3	-8.7, 0.3		0.3, 9.4	-8.1, 0.6	
Open-Label Month 3/Randomization (n)	37	37		37	37	
Mean (SD)	2.92 (2.648)	-3.35 (2.589)	--	3.26 (2.581)	-3.13 (2.098)	--
Min, Max	0.0, 8.9	-8.7, 0.9		0.0, 9.0	-7.4, 0.2	
End of Randomization (n)	37	37	37	37	37	37
Mean (SD)	3.83 (2.775)	-2.44 (3.110)	0.90 (1.550)	3.82 (2.640)	-2.56 (2.465)	0.57 (1.891)
Min, Max	0.0, 9.2	-8.7, 1.9	-2.0, 4.5	0.0, 9.0	-7.8, 4.1	-4.4, 5.9
ANCOVA[4]						0.438

ANCOVA=Analysis of covariance; LOCF=Last observation carried forward; OHDAS=Orthostatic hypotension daily activity scale; OHQ=Orthostatic hypotension questionnaire; OHSA=Orthostatic hypotension symptom assessment; Max=Maximum; Min=Minimum; SD=Standard deviation.

1 OHQ composite score is the average of the OHSA and OHDAS composite scores. The OHSA composite score is the average of Items 1-6 with a score of 1 or more at the Baseline visit. The OHDAS composite is the average of the four items from the OHDAS excluding those with a Baseline value of 'cannot do for other reasons'.

2 Missing data were imputed using the LOCF method.

3 Baseline was the last non-missing value prior to the first dose of study treatment as part of Studies 301 or 302.

4 The p-value from non-parametric ANCOVA using Mantel-Haenszel statistics to compare treatment groups based on rank statistics adjusted for the covariate OHQ composite value at Randomization.

Source: Study report for Study 303, table 11-2, section 11.3.1.1, p. 58

Table 22: Summary of OHSA 1 Score (FAS with LOCF)

	Placebo N=37			Droxidopa N=38		
	Result	Change from Baseline	Change from Randomization	Result	Change from Baseline	Change from Randomization
OHSA Item 1						
Baseline[3] (n)	37			38		
Mean (SD)	6.7 (2.09)			6.5 (1.61)		
Min, Max	2, 10			3, 10		
Open-Label Month 3/Randomization (n)	37	37		38	38	
Mean (SD)	2.7 (2.97)	-4.1 (3.14)		2.6 (2.64)	-3.9 (2.40)	
Min, Max	0, 10	-10, 3		0, 10	-9, 1	
End of Randomization (n)	37	37	37	38	38	38
Mean (SD)	4.0 (3.31)	-2.8 (3.65)	1.3 (2.21)	3.5 (2.87)	-3.0 (2.74)	0.9 (2.39)
Min, Max	0, 10	-10, 3	-4, 5	0, 10	-8, 5	-3, 8
ANCOVA[4]						0.251

Source: Study report Study 303, table 11-7, section 11.3.1.2.3., p. 68

Systolic Blood Pressure
It is apparent from Table 23 that there was no statistically significant different in standing SBP between treatment groups at the end of the double-blind treatment period, indicating a lack of sustained effect on standing systolic blood pressure or a carry over effect of droxidopa. The trend in this experience was counter to what one would expect if droxidopa affects standing systolic blood pressure. Whereas there was no decrease in the standing SBP from Randomization to End of Study in the placebo group, there was an 8.4 mmHg mean decrease in the 3 minute post-standing SBP in the droxidopa group at the End of Study visit compared to the Randomization visit, i.e., the results were exactly counter to those expected.

Table 23: Summary of Systolic Blood Pressure (mmHg) During Orthostatic Stand Test (FAS)

SBP upon Standing +3 Minutes (mmHg)	Placebo N=37			Droxidopa N=38		
	Result	Change from Baseline	Change from Randomization	Result	Change from Baseline	Change from Randomization
Baseline[1] (n)	37			38		
Mean (SD)	89.8 (19.82)	--	--	89.4 (15.22)	--	--
Open-Label Month 1 (n)	37	37		38	38	
Mean (SD)	105.6 (25.39)	15.8 (18.47)	--	100.2 (24.07)	10.8 (22.56)	--
Open-Label Month 2 (n)	37	37		38	38	
Mean (SD)	100.1 (24.19)	10.3 (21.32)	--	97.8 (24.24)	8.4 (24.41)	--
Open-Label Month 3/Randomization (n)	37	37		38	38	
Mean (SD)	101.9 (24.30)	12.1 (20.74)	--	104.1 (24.98)	14.7 (24.38)	--
End of Randomization (n)	37	37	37	38	38	38
Mean (SD)	101.8 (24.20)	12.0 (17.62)	0.0 (18.51)	95.7 (19.81)	6.3 (18.71)	-8.4 (26.63)
p-value[2]					0.162	0.286

ANCOVA=Analysis of covariance; SBP=Systolic blood pressure; SD=Standard deviation.
1 Baseline is the last non-missing value prior to the first dose of study drug as part of Study 301 or 302.
2 The difference between placebo and droxidopa with respect to changes from Baseline and Randomization were evaluated using a non-parametric ANCOVA model using Mantel-Haenszel methodology based on rank statistics adjusted for the Baseline or Randomization value as a covariate.

Source: Study report for Study 303, table 11-3, section 11.3.1.2.1, p. 60

5.3.4 Study 304

Title: A Multi-center, Open-Label Study To Assess the Long Term Safety of Droxidopa in Subjects With Primary Autonomic Failure, Dopamine Beta-Hydroxylase Deficiency, or Non-diabetic Neuropathy and Symptomatic Neurogenic Orthostatic Hypotension

Study Period:
Study Initiation Date: (first patient enrolled): February 19, 2009
Study Completion Date: December 31, 2010

Study 304 is an ongoing open-label extension study of studies 301, 303 (mostly from 302) and another ongoing trial (Study 306) in Parkinson's patients. Enrolled patients were the randomized patients from these former Chelsea Therapeutics, Inc. studies as well as additional patients from these studies who demonstrated a symptomatic response but not the additional BP response during the open-label titration periods. Patients were allowed to be titrated to all doses of droxidopa (100 mg through 600 mg tid). As long as patients met the inclusion criteria for the previous studies and did not meet any of the exclusion criteria, they were allowed to participate in Study 304. There were a total of 213 patients enrolled. Study 304 is considered to be part of the open-label experience and will be reviewed along with the other open-label Chelsea experience (the open-label extension of Study 303) in the safety section of this review.

5.3.5 Study 305

Title: A multicenter, open-label study to assess the effect of droxidopa on 24-hour blood pressure profile in subjects with primary autonomic failure, dopamine-betahydroxylase deficiency or nondiabetic neuropathy and symptomatic neurogenic orthostatic hypotension

Study Period:
Study Initiation Date: June 17, 2009
Study Completion Date: October 29, 2009

Study Design: This was a Phase III, multicenter, open-label, outpatient study designed to evaluate the effect of Droxidopa treatment on the 24-hour blood pressure profile in patients with neurogenic orthostatic hypotension (NOH) associated with Primary Autonomic Failure, Dopamine Beta Hydroxylase Deficiency, or Nondiabetic Autonomic Neuropathy.

All patients who enrolled in Study NOH305 were in the post-titration washout phase of Study 301 and had planned to participate in Study 303. Patients entered Study 305 for baseline (off drug; Visit 1) assessments at least 2 days following completion of their final titration visit of Study 301. Patients were equipped with a 24-hour ambulatory BP monitoring device and returned to the clinic after 24 hours of BP recording for their assessment.

Patients returned to the clinic for Visit 2 (on-drug) assessments after completing approximately 4 weeks of droxidopa treatment under Study 303 or its long-term extension study (304). Upon completion of the Study 303 or Study 304 procedures, vital signs were measured and patients were then equipped with a 24-hour ambulatory BP monitoring device and returned to the clinic after 24 hours of BP recording to have the collected data assessed. Depending on the adequacy of the 24-hour data collected, patients were to repeat their on-drug 24-hour ambulatory blood pressure assessment within 14 days of the initial attempt.

Number of Patients: 20 enrolled, 18 were analyzed.

Enrollment criteria: All patients were included if they were in the post-titration washout phase of study 301 and planned to participate in study 303 as long as their arm circumference was <13 cm or >42 cm and they were not taking vasoconstricting agents.

Dose of Droxidopa: Each patient took 100 mg, 200 mg, 300 mg, 400mg, 500 mg, or 600 mg TID (1-3 capsules TID), with approximately 100 mL (typically half a glass) of water. Patients took their daily study medication in 3 divided doses. Doses were timed such that the first dose was taken upon waking and then taken approximately every 4 hours thereafter, with the final dose taken early enough (i.e., late afternoon) to minimize drug effects during night-time sleeping hours.

Criteria for Evaluation: There was no efficacy analysis for this study. The study was done primarily with the intent of ruling out postural supine night-time hypertension. Descriptive statistical methods were used to summarize the data from the study.

Results: Among all subjects, there was a statistically significant increase of 7.3 mmHg (±11.7) in the 24-hour mean systolic BP (p=0.027) and a significant increase of 4.8 mmHg (±5.71) in the 24-hour mean diastolic BP (p=0.003) in subjects comparing their off vs. on-drug treatment periods. Oddly, there was a small decrease in mean systolic BP measurement (3mmHg) between Visit 1 and Visit 2.

6 Review of Efficacy

Efficacy Summary

3of the 5 clinical trials submitted in this NDA addressed efficacy (301, 302 and 303). It is important to note that due to the enrichment design of the trial accomplished by subjecting patients to a screening/ titration period, 40% of the enrolled patients did not get randomized to the double-blind efficacy assessment periods of the clinical trials.

Study 302 was a randomized withdrawal design study and was completed first. It lost on its primary efficacy endpoint [Orthostatic Hypotension Symptom Assessment, Item 1 (often used as a primary endpoint in trials of orthostatic hypotension to measure clinical benefit)] and failed to show a difference in standing systolic blood pressure (SBP) between placebo and droxidopa at end-of-study. Study 302 is best viewed as a hypothesis generating study. However, the applicant considers it to be a supportive study to Study 301 because it was successful on a post-hoc exploratory analysis of the Orthostatic Hypotension Questionnaire (OHQ), which is comprised of questions of symptoms and impact on functioning, and which later became the primary endpoint for Study 301.

Study 301 was in progress when the results of the 302 exploratory analysis were known. For this reason, the primary efficacy endpoint of study 301 was changed from the OHSA, item 1 score to the entire OHQ. Clinical study 301 is the only study in this NDA that won on its primary endpoint: the OHQ. It also was showed improvement in OHSA Item 1 and an improvement in standing systolic BP.

In clinical trial 303, a 3-month trial ending in a two week randomized withdrawal phase that enrolled patients mostly from 302, there was no difference between active treatment arm and the placebo arm at the end of the two week period in the OHQ scores or the standing SBP. This result suggests that if any effect on symptoms occurs, it may wear off by the end of a 3-month period on drug (development of tolerance). The sponsor's rationale for failure in this study is that there may be a carry-over effect of droxidopa despite its short half-life. The sponsor stated that the study was not sized to demonstrate efficacy- but the pre-IND meeting of May 1, 2007 included a lengthy discussion on the FDA's desire to see durability of effectiveness. Both treatment groups were much improved over baseline OHQ scores, assessed 3 ½ months prior (by approximately 2.5 points). It is unfortunate that longer randomized withdrawal phases were not included in the trial designs for studies 302 and 303.

Study 304 is an ongoing open-label extension study of studies 301, 303 (mostly from 302) and another ongoing trial (Study 306) in Parkinson's patients. Study 305 was a 24 hour ambulatory blood pressure monitor (ABPM) study.

6.1 Indication

One indication is being sought for droxidopa in this application: symptomatic orthostatic hypotension in patients with primary autonomic failure [Parkinson's Disease (PD), Multisystem Atrophy (MSA), and Pure Autonomic Failure (PAF)], Dopamine β Hydroxylase (DBH) Deficiency, or non-diabetic autonomic neuropathy .

6.1.1 Methods

Main Enrollment Criteria

- ≥18 years of age
- Clinical diagnosis of OH associated with primary autonomic failure [Parkinson's Disease (PD), Multisystem Atrophy (MSA), and Pure Autonomic Failure (PAF)], Dopamine β Hydroxylase (DBH) Deficiency, or non-diabetic autonomic neuropathy
- A documented fall in SBP of at least 20 mmHg, or in diastolic BP (DBP) of at least 10 mmHg, within 3 minutes after standing
- Not currently taking vasoconstricting agents such as ephedrine, dihydroergotamine, or midodrine; or antihypertensives or norephinephrine reuptake inhibitors
- No pre-existing sustained severe hypertension (BP ≥ 180/110 mmHg in the sitting position)
- No cardiac arrhythmia, diabetes, or serious systemic, cardiac, renal or hepatic disease

REVIEWER'S COMMENT(S): by restricting the studies to a relatively healthy population, the applicant restricted the noise that could be introduced into the study, improving their likelihood of getting positive results. However, the generalizability of the findings to other patients with symptomatic orthostatic hypotension, particularly elderly patients and patients with diabetes, becomes limited.

Schema

Both phase 3 studies had an up-to-2 week screening phase followed by an up-to- 2 week titration phase during which droxidopa would be titrated up by 100 mg tid every day unless there were side effects that prevented the titration, the SBP increased to > 180mmHg, the DBP increased to > 110mmHg, the patient's OHSA improved to 0 or the dose of 600 mg tid had been attained.

A patient would be randomized into the double blind phase only if he/she had at least 1 point improvement in the OHSA 1 category, and at least a 10 mmHg SBP rise on the orthostatic standing test at 3 minutes without any intolerable side effects and without an increase in SBP to > 180 mmHg and/or and increase in DBP to > 110 mmHg during the orthostatic standing test.

This titration strategy ensured that patients in the double-blind phase were either made symptom-free on droxidopa or were improved and on the highest tolerable dose. This strategy was intended to enrich the patient population with responders.

The main difference between the two phase 3 studies was the 1-week period after the OL titration period. In Study 301, all patients were off drug during that period. In study 302, all patients were on-drug during that period. Following this, patients in both studies were randomized to droxidopa or placebo, in 301 for a 1-week and in 302 for a 2-week period.

In study 301, patients were droxidopa-free for at least one week prior to the 1-week double blind period whereas in study 302, patients were on droxidopa for as many as 5 weeks prior to the 2-week double blind period which was a randomized withdrawal period.

6.1.2 Demographics

The salient demographic features of the studies were as follows:
The mean age range of the patients in the double-blind phases of Studies 301 and 302 was 57.4 (20, 84) and 55.7 (18, 87) for droxidopa-treated and placebo-treated patients respectively. The patients in the OL phase tended to be older than the patients who made it through to the DB phases of the trials. The mean age of patients in the OL run-in phase in studies 301 and 302 was about 67 whereas the mean age of the patient in the DB phases of these studies was only about 60. There was little difference between the droxidopa and placebo arms. The tabular listing of age distribution by study is presented in Table 24.

Table 24: Age Distribution by Study

Criterion	Study	N	Variable	OL	Placebo	Droxidopa	LT OL f-up
Age	301	OL (N=101) Pl (N=81) Dr (N=81)	Mean (SD) Min, Max	64.6 (15.4) 19, 91	55.8 (19.9) 18, 87	57.3 (17.0) 20, 84	
	302	OL(N=80) Pl (N=51) Dr (N=50)	Mean (SD) Min, Max	69.5 (9.7) 37, 86	66.6 (11.25) 40, 88	63.1 (13.76) 24, 88	
	303	OL(N=27) Pl (N=37) Dr (N=38) LT-OL(N=74)	Mean (SD) Min, Max	61.9 (11.0) 40, 88	66.2 (12.09) 30, 88	68.2 (13.03) 30, 86	67.5 (12.43) 30, 88
	304	Dr (N=213)	Mean (SD) Min, Max	61.1 (16.8) 18, 87			
	305	Dr (N=20)	Mean (SD) Min, Max	74 (6.3) 61, 86			

There were generally more men in the double-blind programs than women except in study 301 where the numbers were evenly matched (Table 25).

Table 25: Sex Distribution by Study

Criterion	Study	N	Variable	OL	Placebo	Droxidopa	LT OL f-up
Sex	301	OL (N=101) Pl (N=81) Dr (N=81)	male female	64 (63.4%) 37 (36.6%)	43 (53.1%) 38 (46.9%)	41 (50.6%) 40 (49.4%)	
	302	OL(N=80) Pl (N=51) Dr (N=50)	male female	45 (56.3) 35 (43.8)	32 (62.7) 19 (37.3)	30 (60.0) 20 (40.0)	
	303	OL(N=27) Pl (N=37) Dr (N=38) LT-OL(N=74)	male female	14 (51.9) 13 (48.1)	24 (64.9) 13 (35.1)	23 (60.5) 15 (39.5)	47 (63.5) 27 (36.5)
	304	Dr (N=213)	male female	127 (59.6) 86 (40.4)			
	305	Dr (N=20)	male female	13 (72%) 5 (28%)			

OL= Open Label, Pl= placebo, Dr= Droxidopa

Very few patients of other races than Caucasian were exposed during the development program (Table 26).

Table 26: Race Distribution by Study

Criterion	Study	OL	placebo	droxi
Race	301	98% White 2% Black	93.8% White, 1.2% Black, 1.2% Asian, 3.7% Latino	100% White,
	302	98.8% White 1.2% Black	94,1% White, 2.0% Black, 2.0% Asian, 2.0% Latino	98% White 2% Black

There were fewer people in the US enrolled in the double blind phase of study 301 (65 US vs. 97 OUS). In the double blind phase of study 302, there were 57 patients from US vs. 44 from OUS (Table 27).

Table 27: Geographic Distribution by Study

Criterion	Study	N	Variable	OL	Placebo	Droxidopa	LT OL f-up
Geographic Area	301	OL (N=101) Pl (N=81) Dr (N=81)	US OUS	48 (47.5) 53 (52.5)	33 (40.7) 48 (59.3)	32 (39.5) 49 (60.5)	
	302	OL(N=80) Pl (N=51) Dr (N=50)	US OUS	53 (66.3) 27 (33.8)	32 (62.7) 19 (37.3)	25 (50.0) 25 (50.0)	
	303	OL(N=27) Pl (N=37) Dr (N=38) LT-OL(N=74)	US OUS		22 (59.5) 15 (40.5)	24 (63.2) 14 (36.8)	46 or 45 28 or 29

OL= Open Label, Pl= placebo, Dr= Droxidopa, LT-OL = Long-term Open Label

Approximately 40% of the patients had Parkinson's disease. The rest was mostly split between patients with Multisystem Atrophy and Pure Autonomic Failure. Very few had diagnoses of "nondiabetic nephropathy" or "other" (Table 28). Only one had a diagnosis of dopamine β-hydroxylase deficiency,

Table 28: Primary Diagnosis Distribution by Study

Criterion	Study	N	Variable	OL	Placebo	Droxidopa	LT OL f-up
Primary Clinical Diagnosis	301	OL (N=101)	PD	45 (44.6%)	31 (38.3%)	35 (43.2%)	
		PI (N=81)	MSA	18 (17.8%)	12 (14.8%)	14 (17.3%)	
		Dr (N=81)	PAF	33 (32.7%)	28 (34.6%)	26 (32.1%)	
			DBH Def	0	0	0	
			NDN	2(2.0%)	6 (7.4%)	2 (2.5%)	
			Other	3(3.0%)	4(4.9%)	4(4.9%)	
	302	OL(N=80)	PD	38 (47.5)	23 (45.1)	21 (42.0)	38 (51.4)
		PI (N=51)	MSA	21 (26.3)	13 (25.5)	17 (34.0)	16 (21.6)
		Dr (N=50)	PAF	18 (22.5)	10 (19.6)	8 (16.0)	15 (20.3)
			DBH Def	0	1 (2.0)	0	1 (1.4)
			NDN	2 (2.5)	3 (5.9)	2(4.0)	2 (2.7)
			Other	1 (1.3)	1 (2.0)	2(4.0)	2 (2.7)
	303	OL(N=27)	PD	10 (37.0)	18 (48.6)	20 (52.6)	
		PI (N=37)	MSA	10 (37.0)	9 (24.3)	8 (21.1)	
		Dr (N=38)	PAF	3 (11.1)	7 (18.9)	8 (21.1)	
		LT-OL(N=74)	DBH Def	0	0	1 (2.6)	
			NDN	3 (11.1)	2 (5.4)	0	
			Other	1 (3.7)	1 (2.7)	1 (2.6)	
	304	Dr (N=213)	PD	103 (48.4)			
			MSA	31 (14.6)			
			PAF	66 (31.0)			
			DBH Def	0			
			NDN	7 (3.3)			
			Other	6 (2.8)			
	305	Dr (N=20)	PD				
			MSA				
			PAF				
			DBH Def				
			NDN				
			Other				

PD= Parkinson's disease, MSA= Multisystem Atrophy, PAF= Pure Autonomic Failure, DBH def= Dopamine β-Hydroxylase Deficiency, NDN = Nondiabetic Nephropathy

Mean Baseline OHQ was approximately 6.0 (0 = no symptoms, 10 = worst symptoms) for patients enrolled in the double blind phases of the development program. The baseline OHQ score was similar between treatment groups (Table 29).

Table 29: Baseline OHQ Distribution

Criterion	Study	N	Variable	Placebo	Droxidopa
Baseline OHQ	301	Pl (N=81)	n	79	81
		Dr (N=81)	mean (SD)	5.62(2.0)	5.96(1.7)
			Min, Max	1.2, 9.8	2.0,9.6
	302	Pl (N=51)	n	49	
		Dr (N=50)	mean (SD)	6.04(2.2)	6.22(1.9)
			Min, Max	0.9, 9.5	2.1,9.6
	303	Pl (N=37)	n	37	37
		Dr (N=38)	mean (SD)	6.27 (1.9)	6.38 (1.8)
			Min, Max	2.1, 9.2	3.0, 9.6

Pl= placebo, Dr= Droxidopa

Mean standing SBP + 3 minutes was similar across studies and study groups, approximately 90 mmHg (Table 30).

Table 30: Baseline SBP upon Standing + 3 minutes (mmHg)

Criterion	Study	N	Variable	Placebo	Droxidopa
Baseline SBP upon Standing +3 minutes (mmHg)	301	OL (N=101) Pl (N=81) Dr (N=81)	n mean (SD) Min,Max	80 90.7(16.8) 50,130	82 90.8(15.6) 45,142
	302	OL(N=80) Pl (N=51) Dr (N=50)	n mean (SD) Min,Max	50 88.0 (19.0) 50, 130	50 87.0 (17.6) 37, 116
	303	OL(N=27) Pl (N=37) Dr (N=38)	n mean (SD) Min,Max	37 89.8 (19.8) 64, 185	38 89.4 (15.2) 87, 188

OL= Open Label, Pl= placebo, Dr= Droxidopa

6.1.3 Subject Disposition

62% and 56% of the enrolled patients met the selection criteria and were enrolled in the double blind period in Studies 301 and 302, respectively (Table 31).

Table 31: Enrollment in Studies 301 and 302

Study	Number Enrolled	Number enrolled in DB
301	263 (101 OL only)	81 placebo 81 Droxidopa
302	181 (80 OL only)	51 placebo 50 Droxidopa

Patients dropped out from the protocol primarily because they were treatment failures or because they had adverse events. Very few patients dropped out once they had met the criteria for enrollment into the double-blind phase, not surprising given the short length of the DB periods. Using the sponsor's individual patient disposition charts I constructed Table 32 to analyze the disposition of the patients. Most patients who did not go on to

be randomized were treatment failures which could mean that they had reached the 600 mg tid dose without a treatment benefit, had an AE related to dose titration or BP goals for discontinuation were met.

Table 32: Disposition of Study 301 and Study 302

	OL Phase	DB Phase	
		Placebo N=135	Droxidopa N=134
Total Patients Treated	181		
All Patients Randomized		135	134
Patients randomized and treated in DB phase		131 (97.0)	132 (98.5)
Completed Study Per Protocol		119	125
Completed DB Phase (> 6 days for 301 and > 11 days for 302)		121 (89.6)	131 (99.2)
Reason for Discontinuation (from Per Protocol)			
Treatment Failure	107 (58.6)	6 (50)	1 (14.2)
Adverse Event	25 (13.8)	2 (16.7)	1 (14.2)
Protocol Violation	9 (5.0)	3 (25)	3 (42.9)
Withdrew consent	11 (6.1)	0	
No symptoms	1 (0.6)	0	
Noncompliance	1 (0.6)	0	1 (14.2)
Misunderstanding	0	1 (8.3)	1 (14.2)
Investigator Decision	2 (1.1)	0	
Randomization limit/ Sponsor decision	15 (8.3)	0 0	
Titration failure	2 (1.1)	0	
Missing*	5 (2.8)	0	
High BP	1(0.6)	0	

*** (study 301) site considered them complete but they were not considered to be complete**

6.1.4 Analysis of Primary Endpoint(s)

The primary efficacy end point for Study 301 was change in OHQ. A negative number is an improvement. The placebo subtracted result for the change in OHQ for Study 301 was -0.90. In Study 302, the placebo subtracted result for the change in OHQ (a post-hoc exploratory analysis) was -1.11. In Study 301, the placebo arm also improved by -0.93 points compared to randomization. In Study 302, the placebo arm OHQ score worsened by 1.22 after two weeks of withdrawal from five weeks of droxidopa treatment.

These trials seem to support the efficacy of droxidopa in patients with symptoms of NOH from PD, MSA, PAF, dopamine β hydroxylase deficiency and nondiabetic neuropathy over a 1 or 2 week period. Beyond that, there is no supportive efficacy data. Study 303 which enrolled patients from study 302 mostly and continued them on droxidopa for 3 months followed by a 2 week randomized withdrawal period showed no difference in the OHQ between the placebo and the droxidopa group. The sponsor claims that the study was not powered to be able to show a difference. The trend for Study 303 was that the droxidopa group did not worsen as much as the placebo group on the OHQ but the point difference was only 0.33. This difference is negligible and should be interpreted as a negative study and if anything suggests that the effect of droxidopa on symptoms of neurogenic orthostatic hypotension is not durable. The results of Study 303 are displayed in Table 21 in Section 5.

Table 33: OHQ for Study 301 and Study 302

			Placebo			Droxidopa			
Study			**Randomization**	**End of Study**	**Δ**	**Randomization**	**End of Study**	**Δ**	**p-value**
301	Pl (N=80)	N	79	79	79	81	81	81	0.003*
	Dr (N=82)	Mean (SD)	4.97 (2.41)	4.04 (2.61)	-0.93 (1.69)	5.11 (1.96)	3.29 (2.20)	-1.83 (2.07)	
		Min, Max	0.7, 9.8	0.0, 9.8	-7.5, 2.6	0.9, 9.1	0.0, 8.4	-6.2, 4.4	
302	Pl (N=51)	N	49	51	49	47	50	47	0.013**
	Dr (N=50)	Mean (SD)	2.83 (2.26)	3.91 (3.02)	1.22 (2.39)	2.93 (2.12)	3.16 (2.54)	0.11 (2.18)	
		Min, Max	0.8.1	0,9.4	-4.2, 7.8	0, 7.7	0, 9.5	-5.3, 7.7	

* ANCOVA used. The model included a factor for randomized treatment along with the OHQ composite value at Randomization as a covariate

** The changes from Randomization were evaluated using one-sided Wilcoxon rank

The OHQ is not an acceptable primary efficacy endpoint. It is comprised of a set of 6 symptom questions (OHSA 1 - 6) and a set of 4 functional questions (OHDAS 1-4). Dr. Elektra Papadopoulos of the Study Endpoints and labeling Development Division (SEALD) of the FDA did a thorough review of this Patient Reported Outcomes Measure and concluded that the OHQ was not sufficient for describing the impact of droxidopa on symptomatic orthostatic hypotension. I agree with her assessment for the following reasons:

1. The OHDAS questions should have been crafted to measure the functional impact on the symptoms of orthostatic hypotension. It should have included questions that specifically addressed symptoms associated with postural changes and ability to make those postural changes during their daily activities. Instead, it just queried the patients regarding the ability to stand and/or walk.
2. The OHSA questions should have been crafted to measure the symptoms that were derived from the qualitative research as most important and bothersome to the patients interviewed. The OHSA questions do not assess some symptoms that were discovered in the qualitative research included in the review (imbalance and falling, for instance). Conversely, some of the OHSA questions assessed some extraneous symptoms that were not discovered in the qualitative research to be most troubling to the patients (difficulty concentrating and head/ neck discomfort). Furthermore, the OHSA question regarding “fatigue” was ambiguous as fatigue can mean weakness or tiredness. Most patients were discovered in the qualitative research to suffer more from tiredness than fatigue.

The OHSA Item 1, on the contrary, captures the most important symptoms of the patients who suffer from symptomatic orthostatic hypotension: dizziness, lightheadedness, feeling faint, or feeling like you might black out. The concept of OHSA Item 1 is comprehensive and unambiguous. The symptom assessed by this item is a core symptom of symptomatic neurogenic orthostatic hypotension as assessed by the qualitative research and therefore has content validity. Although the OHSA Item 1 is acceptable for measuring symptoms and was used in the midodrine development program, OHSA Item 1 is still not ideal because it is not context dependent. Patients could be dizzy without postural changes or with postural changes. It would be better to be able to distinguish between these two possibilities.

Study 301, when analyzed using OHSA Item 1 as the primary efficacy endpoint showed extremely favorable results as shown in Table 34 and Figure 13. However, the efficacy results of Studies 302 and 303 when analyzed using OHSA Item 1 as the primary efficacy endpoint are negative. The results do lean in favor of drug [the difference in OHSA Item 1 between placebo and droxidopa treated patients

were 0.6 (p = 0.51) and 0.4 (p=0.25) points for Study 302 and Study 303, respectively as shown in Table 14 and Table 22], but these are minimal effect sizes and not statistically significant. It is hard to believe that the results indicate any real benefit because the SBP went in the wrong direction in both studies.

Table 34: OHSA Item 1 Results for Study 301

OHSA Item Symptom	Placebo, Mean (SD) N=80			Droxidopa, Mean (SD) N=82			ANCOVA[2]
	Randomization	End of Study	Δ	Randomization	End of Study	Δ	
Item #1 (n)	80	80	80	82	82	82	
Dizziness	5.4 (2.88)	4.3 (3.10)	-1.1 (2.58)	5.4 (2.46)	3.0 (2.67)	-2.4 (3.20)	<0.001

Source: Study 301 Study Report, Table 11-7, Section 11.4.1.1.1., p. 66

It is possible that the failure of Study 302 and Study 303 is reflective of the lack of effectiveness of droxidopa and Study 301 has given us erroneous results

The sponsor has suggested that the failure of Study 303 (where there was a 3-month OL droxidopa treatment period followed by a 2-week randomized withdrawal period) was due to a carry-over effect of droxidopa. The idea behind this carry-over effect is that the effect of droxidopa is much longer lasting than the half-life would suggest. This is an attractive idea and one might consider suggesting that Study 302 (where there was a 5 week OL droxidopa treatment period followed by a 2-week randomized withdrawal period) failed as well on this basis. If there is truly a carry-over effect of droxidopa, it may have also affected the results of Study 301. Had the patients not been exposed to droxidopa during the OL titration phase perhaps the difference in results of the OHSA Item 1 and OHQ between the treatment groups would have been even more dramatic.

An alternative hypothesis to explain the failure of Studies 302 and 303 on the OHSA Item 1 endpoint is that droxidopa may continue to work but patients may experience an even greater benefit from nonpharmacological interventions. The benefit from the nonpharmacological interventions may lessen the relative benefit of droxidopa, making it more difficult to demonstrate benefit in a clinical trial setting. Perhaps after getting the patient out of bed and doing basic exercises needed for getting to the clinic and optimizing other nonpharmacological treatments such as volume expansion, certain intrinsic mechanisms of homeostasis become activated and symptoms and performance improve so much that the marginal additive improvement from the vasoconstricting agent (droxidopa) becomes less.

Nonpharmacological treatments have been anecdotally reported to have remarkable therapeutic benefits in this patient population. Alexander MacLean and Edgar Allen published an article in JAMA in December, 1940[15] where they described 2 patients with debilitating neurogenic orthostatic hypotension who improved dramatically by tilting the heads of their beds up by approximately 30 degrees. The investigators were able to demonstrate dramatic improvement in daytime orthostatic blood pressure readings and remission of syncope and presyncopal symptoms. After having the patients resume their usual flat sleeping positions, they relapsed. One of the two patients went from being bedridden to working 6 hours a day in the office and 2 hours a day in the garden. These case reports suggest that other nonpharmacological factors may have played a role in the overall improvement in the patients in these studies.

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6.1 .5 Analysis of Secondary Endpoints(s)

The results of the secondary endpoints were listed in the individual study reports in Section 5 of this review. None of these analyses are helpful for deciding upon approvability and therefore will not be discussed again in this section.

6.1.7 Subpopulations

I have combined studies 301 and 302 for the purpose of discussing the subgroup analyses. Certain subpopulations received more benefit as measured by OHQ score on droxidopa than others. In Table 35, one can see that while the trend was for improvement in all diagnostic groups, the patients with MSA and PAF seemed to derive more benefit than patients with PD.

Table 35: Outcome by Underlying Diagnosis, Study 301 and 302 combined

	Placebo, Mean, (SD)	Droxidopa, Mean, (SD)		
Subgroup	**Δ**	**Δ**	**placebo subtracted difference**	**p-value**
PD, n	52	56		
	-0.18	-1.02	-0.84	0.085
	(2.14)	(2.16)		
MSA, n	22	28		
	0.14	-1.02	-1.16	0.018
	(2.39)	(1.81)		
PAF, n	38	34		
	-0.26	-1.54	-1.28	0.022
	(2.35)	(2.9)		
NDN, n	9	4		
	-0.16	-1.82	-1.66	0.331
	(2.49)	(2.67		
Other, n	5	5		
	0.76	0.75	-0.01	0.931
	(2.77)	-1.1		

In Table 36, one can see that there was a larger effect size in the U.S. treated patients.

Table 36: Outcome by Region in Study 301 and 302 Combined

	Placebo, Mean, (SD)	Droxidopa, Mean, (SD)		
Subgroup	**Δ**	**Δ**	**placebo-subtracted difference**	**p-value**
US, n	62	55		
	0.39	-0.77	-1.16	0.02
	(2.68)	(2.52)		
OUS, n	66	72		
	-0.58	-1.38	-0.8	0.018
	(1.66)	(1.12)		

In Table 37, one can see that there is no effect of droxidopa in patients ≥75 years of age and that most of the effect is see in patients < 65 years of age.

Table 37: Outcome by Age in Study 301 and 302 Combined

	Placebo, Mean, (SD)	Droxidopa, Mean, (SD)		
Subgroup	**Δ**	**Δ**	**placebo subtracted difference**	**p-value**
<65 years, n	69	71		
	-0.03	-1.48	-1.45	<0.001
	(2.42)	(2.04)		
>= 65 years, n	58	56		
	-0.19	-0.65	-0.46	0.335
	(2.07)	(2.56)		
>= 75 years, n	31	23		
	-0.12	-0.04	0.08	0.914
	(2.30)	(2.58)		

In Table 38, a larger effect size is seen in the male patients.

Table 38: Outcome by Sex in Study 301 and 302 Combined

	Placebo, Mean, (SD)	Droxidopa, Mean, (SD)		
Subgroup	Δ	Δ	placebo subtracted difference	p-value
Male, n	71 -0.02 (2.12)	70 -1.33 (2.06)	-1.31	<0.001
Female, n	56 -0.21 (2.44)	57 -0.86 (2.59)	-0.65	0.095

In Table 39, one can see that patients with OHQ scores of median or worse at baseline (~ 6), may have been more likely to respond to droxidopa. In Study 301, the patients with lower Baseline OHQ scores improved more than patients with higher Baseline OHQ scores.

Table 39: Outcome by Baseline OHQ in Study 301 and 302 Combined

	Placebo, Mean, (SD)	Droxidopa, Mean, (SD)		
Subgroup	Δ	Δ	placebo subtracted difference	p-value
Lower than median OHQ score, n	65 -0.14 (1.95)	59 -1.06 (2.36)	-0.92	0.192
Higher or equal to median OHQ score, n	62 -0.07 (2.57)	68 -1.17 (2.29)	-1.1	<0.001

6.1.10 Additional Efficacy Issues/Analyses

6.1.10.1 Minimal Effective Difference

The SEALD team reviewer, Dr. Elektra Papadopoulos, reviewed the data that the sponsor submitted to justify their conclusion that the minimal clinically important intrapatient difference in the OHQ score was between 0.6 and 0.9 units. The sponsor's analytical methods were in accordance with the guidance for evaluating Patient Reported Outcomes Measures in that the sponsor took into consideration both the anchor-based as well as the two-distribution based methods. The problem, however, was that the sponsor used data drawn from a previous study using midodrine hydrochloride instead of the data at hand. Dr. Papadopoulos's opinion is that the current droxidopa studies (Study 301 and Study 302) are the preferable sources of data for estimating the intrapatient change in score that should be considered meaningful in those studies.

The droxidopa clinical trials used four different global impression scales; two of these were clinician-reported and the other two were patient-reported. Given that only patients can validly report their symptoms, Dr. Papadopoulos recommends that only the patient-reported scales be considered as anchors. The patient-reported CGI-I asks subjects to compare their current state with Visit 2 (baseline, prior to the dose titration period). The patient-reported CGI-S is simply measured at a single point in time and does not require any comparison to another timepoint. The relatively simple task of reporting on a discreet timepoint (as with the CGI-S) is likely more valid than a more complex task that requires comparison to a previous timepoint. Additionally, given that the trial included two treatment periods separated by a washout period, there is even greater risk of error and potential misunderstanding in what patients should use as the reference point when evaluating their change. Therefore, this reviewer recommends that the anchor-based methods using changes on the patient-reported CGI-S should be given the most weight for interpretation of meaningful intra-patient changes.

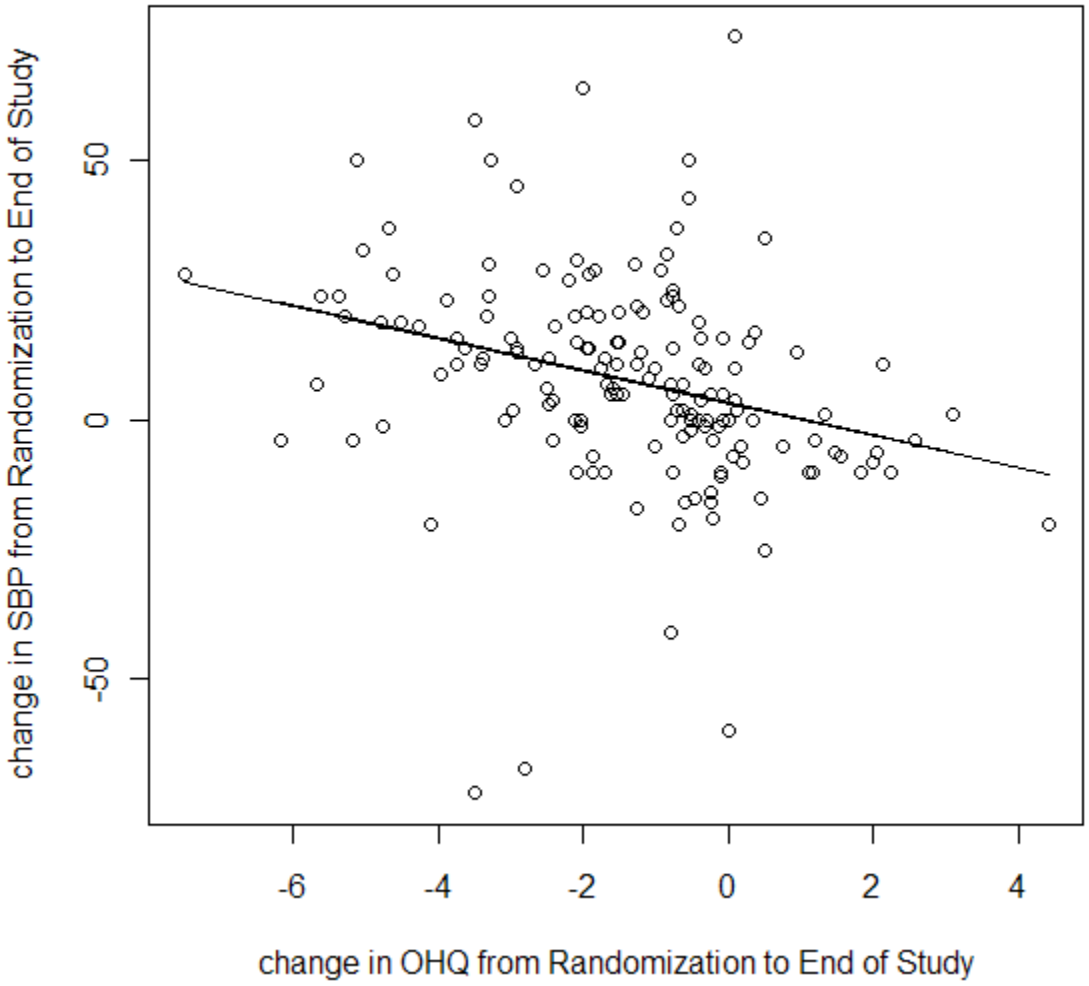
The sponsor was asked to do CGI-S (by Patient) anchored analyses for both OHQ and OHSA Item 1 using the data in Study 301 and Study 302. Without these analyses it is difficult to assess the clinical significance and strength of the effect sizes seen in this development program.

6.1.10.2 Relationship between change in SBP and change in scores on OHQ and OHSA Item 1

The statistics reviewer, Dr. Jialu Zhang explored the relationship between change in SBP and change in scores on the OHQ and OHSA Item 1 between Randomization and End of Study for Study 301. The linear regression lines have R^2 values of 0.09 and

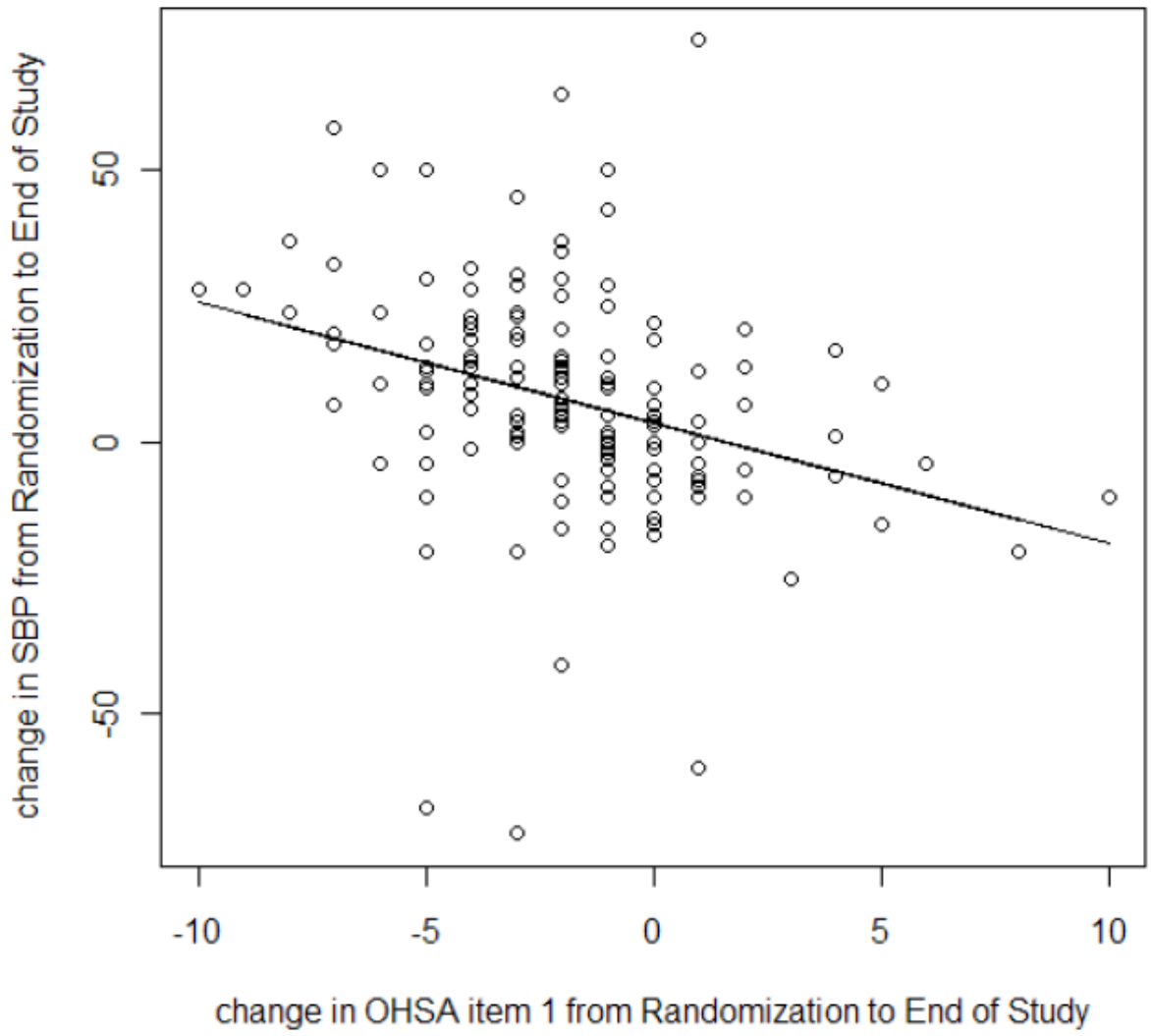
0.11, indicating that there is no correlation between change in SBP and OHQ (Figure 20) or OHSA Item 1 (Figure 21).

Figure 20: Relationship between Change in SBP in mmHg and Change in OHQ from Randomization to End of Study for Study 301



R2 = 0.09, slope =-3.1 (1 unit decrease in OHQ corresponds on average to a 3.1 mmHg systolic blood pressure increase)

Figure 21: Relationship between Change in SBP in mmHg and Change in OHSA Item 1 from Randomization to End of Study for Study 301



R2 = 0.11, slope =-2.2 (1 unit decrease in OHQ corresponds on average to a 2.2 mmHg systolic blood pressure increase)

7 Review of Safety

Safety Summary

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The safety data are divided into double-blind exposure data and open-label data. Studies 301, 302 and 303 include both. Study 304 contributed only to the open-label data. These studies are described in detail in section 5.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

The total patient exposure in the Chelsea program was 535 patients with 276 patients exposed ≥ 6 weeks and only 64 of those were exposed to the maximum dose of 600 mg tid. 93 patients only were exposed over 1 year and only 26 of those were exposed at the maximum dose of 600 mg tid. There was limited phase 3 double-blind exposure; only 131 patients received droxidopa with a mean exposure of 11 days during the double-blind phase 3 studies. This low degree of long-term exposure makes it difficult to evaluate properly the long-term safety of droxidopa. Additionally, the limited exposure to the highest dose, 600 mg tid, makes it difficult to make a proper safety assessment (Table 40).

Table 40. Exposure

	Duration of Exposure to Droxidopa				
	<6 weeks	≥6 weeks	≥3 months	≥6 months	≥1 year
Total Daily Dose (mg):					
300	45 (100.0)	9 (20.0)	7 (15.6)	4 (8.9)	3 (6.7)
600	74 (100.0)	41 (55.4)	28 (37.8)	20 (27.0)	11 (14.9)
900	96 (100.0)	53 (55.2)	50 (52.1)	45 (46.9)	14 (14.6)
1200	125 (100.0)	61 (48.8)	58 (46.4)	47 (37.6)	17 (13.6)
1500	70 (100.0)	48 (68.6)	39 (55.7)	32 (45.7)	22 (31.4)
1800	66 (100.0)	64 (97.0)	58 (87.9)	44 (66.7)	26 (39.4)
Total Number of Patients	**476 (100.0)**	**276 (58.0)**	**240 (50.4)**	**192 (40.3)**	**93 (19.5)**

Subjects enrolled in Studies 101 and 102 are not counted in this table.
Source: ISS Table 1.2.2.3 (Section 11.13).

7.2.4 Routine Clinical Testing

Blood pressure was not measured when patients were fully supine. This is problematic because supine hypertension is a potential safety issue with droxidopa. It would have been helpful to have occasional blood pressure readings when the patients were fully supine to evaluate the magnitude of the effect of droxidopa on supine blood pressure for purposes of safety labeling.

7.2.5 Metabolic, Clearance, and Interaction Workup

Droxidopa and its metabolites are predominately cleared by the kidney. Patients with decreased renal function have increased exposure to droxidopa and a potential for increased AEs. The incidence of AEs was not different across GFR quartiles (estimated by serum creatinine clearance). An additional analysis using clinical cutoff for GFR <60 mL/min versus GFR >60 mL/min at Baseline also showed no meaningful differences in AE reporting between droxidopa- and placebo-treated patients in these GFR categories.

Greater than 85% of patients used droxidopa in combination with concomitant medications in both the placebo-controlled study grouping and the long-term extension study grouping, and the most common concomitant medications were DOPA and DOPA-derivatives (>49%), fludrocortisone (>29%) and platelet aggregation inhibitors (>26%). Since most of the AE collection in these trials was uncontrolled, it is difficult to assess if these drugs when given concomitantly with droxidopa will increase the risk of AEs. Theoretically, carbidopa can interfere with the conversion of droxidopa to NE and

therefore impair efficacy. Theoretically, droxidopa, by competing with DOPA decarboxylase in the central nervous system could decrease the effectiveness of levodopa.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Fludrocortisone is associated with the adverse events that were also seen commonly in the droxidopa safety data base: headaches, fractures, weakness and vertigo.

Carbidopa and Levodopa are associated with the following adverse effects also seen in the droxidopa safety data base: hypotension, and orthostatic hypotension, syncope, palpitations, gastrointestinal upset including pain, constipation and diarrhea, and vomiting, leucopenia, hallucinations, muscular pain, urinary tract infection and retention, malaise, increased creatinine and decreased white blood cell count.

Entacapone (given with carbidopa and levodopa) is associated with dyskinesia, dizziness, nausea, diarrhea, and abdominal pain

7.3 Major Safety Results

7.3.1 Deaths

There was 1 death during study 302 and none during study 301. There were 18 deaths plus one failed suicide attempt in all in the Chelsea program. There are a few salient points that bear mentioning. It is important to note that patients with multiple system atrophy have a poor prognosis. Most patients who died had this baseline illness suggesting that the deaths may be more likely related to the underlying condition than the drug. That said, one cannot rule out the possibility of an interaction between the drug and MSA that could hasten death. There are insufficient data to assess this possibility.

- 11/18 had MSA
- 1/18 did not receive droxidopa
- 2/18 died from complications of breaking hip and pelvis, respectively
- 1/18 probably had strokes on therapy (post-mortem exams)
- 1/18 suicide. 55 year old woman was the youngest death. She had MSA and was thought to have committed suicide. There was also one incomplete suicide.
- 5/18 had aspiration pneumonia.
- 1/18 died of cardiopulmonary arrest. The patient had BP of 224/114 but was only on droxidopa for 2 days and then switched to midodrine. She died 11 days later of cardiopulmonary arrest.

- 5/18 patients died of known or suspected sudden death.
- 1/18 patient died of myocardial infarction

The following is a list of deaths that occurred in the Chelsea development program.

1. 58 y/o male with MSA died of “unknown cause” but never received droxidopa
2. 68 y/o female with MSA and Parkinson’s had cardiopulmonary arrest 13 days after starting droxidopa and 11 days after discontinuing therapy (BP was 224/114). Patient was on midodrine at time of death. This could be considered “sudden death”.
3. 63y/o female with MSA died of sudden cardiac death 285 days after initiating droxidopa. BP was 108/70 and HR was 85 bpm 2 weeks before her death
4. 81 y/o female with PD died of acute respiratory failure 437 days after initiating droxidopa therapy and 7 days after discontinuing droxidopa therapy. She experienced a hip fracture, developed serious complications including enteral-vascular fistulas and ARDS. She ultimately died of respiratory failure
5. 88 y/o male with PD died of complications from compound fracture of pelvis 253 days after initiating therapy with droxidopa. The patient fell at home and died 7 days later from complications
6. 60 y/o male with MSA died of hypoxic encephalopathy 85 days after initiating droxidopa therapy. On day 70 the patient ”stopped breathing at home”, was intubated and found to have a cardiac arrhythmia. EEG showed seizure activity. The droxidopa was discontinued but the patient died 15 days later.
7. 57 y/o male with PD died of pneumonia 567 days after initiating droxidopa and 20 days after discontinuing droxidopa therapy. He fell on the first day of therapy and then started on a progressively down hill course culminating in severe aspiration pneumonia
8. 56 y/o female with MSA died of circulatory collapse 127 days after initiation of droxidopa therapy and 6 days after discontinuing droxidopa therapy. She was in hospice care starting 1 month after starting droxidopa. She developed pneumonia and sepsis
9. 70 y/o female with MSA died of acute respiratory failure 446 days after initiating droxidopa therapy and 4 days after discontinuing droxidopa therapy. The patient had aspiration pneumonia
10. 80 y/o male with PD died of cardiac arrest 36 days after initiating droxidopa therapy and 1 day after last dose of droxidopa therapy. No information on BP. Laboratory reports were normal. This could be considered “sudden death”.
11. 57 y/o male with MSA died of progression of multiple system atrophy 145 days after initiating droxidopa therapy and 42 days after discontinuing droxidopa therapy. He had a steep decline in his symptoms. The autopsy showed subacute cerebral infarction of left medial fronto-temporal lobe in process of resolution. It is possible that this event precipitated his death
12. 79 y/o male with MSA died of sepsis 471 days after initiating droxidopa therapy and 20 days after discontinuing droxidopa therapy. The patients had aspiration pneumonia and deteriorated

13. 60 y/o female with MSA and ischemic heart disease died of pneumonia 184 days after initiating droxidopa therapy and 12 days after discontinuing droxidopa therapy. She had 2 AEs of "Periodical increase of arterial pressure" prior to the development of pneumonia, hemorrhagic infarction of the lung and ARDS
14. 61 y/o male with MSA died of respiratory failure 599 days after initiating droxidopa therapy. He started to have difficulty walking, seizures and difficulty swallowing. A few weeks prior to death he was switched from droxidopa to midodrine and died of complications of urosepsis. Autopsy showed subacute cerebral infarction and thrombosis of left carotid artery.
15. 55 y/o female with MSA died of brain edema 599 days after initiating droxidopa therapy. She had bradykinesia, tremor and ataxia at screening. She developed atrial fibrillation, and droxidopa was discontinued but she went into a coma. Suicide was suspected.
16. 78 y/o male with PD died of unknown cause 461 days after initiating droxidopa therapy and discontinued during a change in living arrangements 21 days before his death. This could be considered "sudden death".

Submitted Post-NDA submission

17. 76 y/o male with NDAN enrolled in study 304. The patient was on droxidopa 400 mg tid for 7 months and then and had a myocardial infarction that resulted in the patient's death. He had hyperlipidemia and Amyloidosis as baseline characteristics. During the trial, the patient had 2 SAEs during Study 303 (DVT and dehydration and 5 SAEs in Study 304 (urinary retention, pneumonia, weakness and pancytopenia, and bilateral pleural effusion).
18. 65 y/o female with "autonomic failure". The patient had been on droxidopa for 2 years. She had just started treatment with Sinemet approximately 2 weeks prior to death. The cause of death was unknown at the time of the report. This could be considered to be "sudden death".

Additionally, there was a patient with a failed suicide attempt that was a very serious attempt and almost successful. The 59 y/o patient tried to commit suicide by hanging himself but the rope broke. He was apparently having difficulty dressing and walking. The patient had been on droxidopa for 7 months and had been complaining of worsening of Parkinson's symptoms and his wife had noticed symptoms of depression over the previous month.

Deaths in non-Chelsea-sponsored studies

1. 43 y/o with sever muscle atrophy (familial amyloid polyneuropathy) from complications of urosepsis.
2. 43 y/o with FAP had sudden death after CVA that occurred 178 days after initiating droxidopa.
3. 53 y/o female with FAP died of cardiac and respiratory arrest 81 days after initiating droxidopa. Died of complications of a knee infection after "a traumatic injury"
4. 35 y/o male with FAP died of sudden death 181 days after initiating droxidopa.

5. 30 y/o male with FAP died of septic shock from a UTI 124 days after initiating droxidopa.
6. 28 y/o male with FAP died of sudden cardiac death 18 days after initiating droxidopa and 4 days after discontinuing. He seemed to have improved on treatment. He awakened the day of death with muscle pain and fever. Later he had a cardiac and respiratory arrest. He was homozygous for the TTR Met30 gene.
7. 41 y/o female with FAP who died of pacemaker complications 187 days after initiating droxidopa.
8. 57 y/o male with MSA with sleep apnea died of cardio-respiratory arrest 51 days after initiating droxidopa and 15 days after discontinuing droxidopa. He had a cardiac arrest while on droxidopa and then developed pneumonia a heart failure.
9. 57-year-old male with MSA (2000) died of aspiration 261 days after initiating droxidopa
10. 55-year-old male with MSA (1999), died of a probable myocardial infarction 436 days after initiating treatment with droxidopa
11. 73-year-old male with PD (2000) died of further impairment of general physical status 293 days after discontinuing treatment with droxidopa
12. 60-year-old female with MSA (1996) died of acute respiratory failure after 587 days of droxidopa
13. 62-year-old female with MSA (1997) died of bronchopneumonitis 710 days after initiating treatment with droxidopa
14. 58-year-old female with MSA (1999) died of pneumonia 137 days after initiating treatment with droxidopa
15. 61-year-old female with MSA (1999) died of pneumonia 407 days after initiating treatment with droxidopa
16. 79-year-old male with MSA (1994) died of pyelonephritis 104 days after initiating treatment with droxidopa
17. 72-year-old female with PD (1996) died of a coma 786 days after initiating treatment with droxidopa

7.3.2 Nonfatal Serious Adverse Events

Overall, a total of 60 of 476 (12.6%) patients reported 116 SAEs across Studies 301, 302, 303, and 304.

During the RCT phase of the placebo-controlled study grouping, no droxidopa-treated and 1 (0.8%) placebo-treated patient reported 2 SAEs (mental status change and urinary tract infection). Both events were moderate in severity, required no change in study treatment, and resolved. Even though the patient was on placebo when the event occurred, it must be kept in mind that the patient had been exposed to droxidopa during the titration phase.

The overall incidence of SAEs was also low in the open-label titration phase of the

placebo-controlled studies. Six (1.4%) droxidopa-treated patients reported 10 SAEs. Most events were moderate in severity, unlikely or not related to study drug, required no change in study treatment, and resolved. Three patients discontinued study drug due to SAEs (one for nausea and vomiting; one for coronary artery disease; and one for pneumonia).

In the long-term extension studies, 54 of 301 (17.9%) patients reported 104 SAEs. Study drug was discontinued in 24 of 54 (44.4%) patients with SAEs. The most commonly reported SAEs were syncope (7 patients, 2.3%), pneumonia (5 patients, 1.7%), sepsis (3 patients, 1.0%), and hip fracture (3 patients, 1.0%). It is important to keep in mind that the patient population studied is likely to be susceptible to syncope, falls and hip fracture. Many patients are also sedentary and therefore more susceptible to pneumonia and sepsis. However, since this is an uncontrolled experience, it is not possible to assess drug relatedness and the possibility that droxidopa could be increasing the risk for some of these AEs should not be overlooked.

A line listing of the SAE narratives from the study reports and post-NDA submission safety reports is included in Appendix B.

7.3.4 Significant Adverse Events

AEs Resulting in Discontinuation

In Study 301, 13 (4.9%) patients in the open-label phase had treatment-emergent AEs that led to study discontinuation. The most common AE leading to discontinuation was nausea (4 patients), followed by hypertension (3 patients). The remaining AEs leading to discontinuation (vomiting, asthenia, irritability, dizziness, tremor, palpitations, BP increased, and diabetes mellitus) each occurred in 1 patient.

There was one additional patient who had ongoing hypertensive episodes identified at Screening. This event eventually led to discontinuation, which coincided with additional AEs of palpitations and headache.

In Study 302, 13 (7.2%) patients in the open-label phase and 2 (3.9%) placebo-treated patients in the double-blind controlled phase had AEs that led to study discontinuation. In the open-label phase the most common AE leading to discontinuation and the only individual AE reported by more than 1 patient was dizziness (reported by 3 patients). Other AEs that led to study discontinuation in the open-label phase were troponin increase, angina pectoris, coronary artery disease, ocular hyperemia, pneumonia, dehydration, atrial flutter, hypertension, visual field defect, and palpitations. Two placebo-treated patients in the double-blind phase had an AE that led to discontinuation (loss of consciousness and syncope).

Blood Pressure Related AEs

There were a total of 10 AEs in Study 301 related to hypertension or BP increase. None were SAEs. 3 patients were discontinued and 3 patients had their doses decreased. 5/10 also had headache and 2 had dizziness. 4 were on 600 mg tid when the AE occurred.

In study 302, 3 (1.7%) patients in the open-label phase had AEs of hypertension. 1 had headache and chest pain and another had chest pain.

In study 304, 12 (5.6%) patients had AEs of hypertension. There were 3 AEs of hypertensive crisis according to the sponsor, two that were serious that resolved with treatment (2 had droxidopa discontinued and 1 had dose reduction).

Strokes
One patient, a 68 y/o female with Parkinson's disease had a small vascular stroke on droxidopa after 3 months on droxidopa 400 mg tid. Cardiac risk factors were that the patient had a history of hypercholesterolemia, diabetes and a history of small vessel atherosclerotic disease with an MRI form June 1, 2010 that showed chronic cerebral ischemic white matter changes. The patient's blood pressure was not reported.

There were 2 patients in the OL studies that had TIAs.

Cardiac Complications
There were 10 cases of elevated blood CK in the OL studies, 9 cases of angina but no myocardial infarctions were reported. A few of the deaths were thought to be from myocardial infarction. There were 4 deaths from cardiac arrest.

Worsening of Parkinson's disease or Multisystem Atrophy
There were 2 cases of worsening motor symptoms in patients during the double blind phase of Study 302. Both patients were on droxidopa. There were 31 cases of worsening motor symptoms during the OL periods of the 5 studies. 2 of these were SAEs because of prolonged hospitalizations. It is very difficult to assess if these adverse events were related to droxidopa treatment. 2 cases in the double-blind experience is insufficient to draw any conclusions and the OL experience may reflect the baseline progression of disease in this very ill patient population. Nevertheless, without a longer term placebo-controlled experience, one cannot rule out the possibility that droxidopa could worsen patients' underlying neurological conditions. Theoretically, droxidopa could interfere with the conversion of levodopa to dopamine in the central nervous system by competing with DOPA decarboxylase. Also possible, there could be central nervous system toxicity via DOPAL.

7.3.5 Submission Specific Primary Safety Concerns

A thorough assessment of safety is very challenging given the way the droxidopa development program was structured. While droxidopa is intended as a treatment for a

chronic condition, there was a paucity of long-term safety experience and the long term experience was not placebo-controlled.

Another challenge is that all patients were exposed to drug. Therefore, if there were a delayed adverse event, it is conceivable that the event could occur while the patient was on placebo but truly be related to drug. This could result in an underestimation of the risks of the drug. To make matters worse, the amount of time that the patients were observed in the placebo-controlled phase was low (only one or two weeks) with only one or two visits for capturing AEs. This could lead to an artificially low estimation of AE rate. Moreover, in study 302, AEs that began during the titration phase and persisted into the placebo-controlled phase might not be reported again. They might just be reported as "ongoing." In study 301, there was a 1-week washout, so this seems a little less likely. Also, only 60% of the enrolled patients were randomized and approximately 20% of the patients were not enrolled because of tolerability issues. If droxidopa were to be approved, the AE rate would likely be higher than what was seen in the trials.

During the uncontrolled extension trials, the exposure to the higher doses of droxidopa was higher than the exposure to the lower doses. The sponsor realized this and calculated AE rates based on patient years of exposure. This was the appropriate way to analyze these data. Unfortunately, with all the different dosing regimens (6), the amount of exposure for each of the 6 dosing regimens was relatively low and therefore the data may not provide as reliable an estimate of adverse event rates as one would like.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

During the randomized controlled parts of the development program, the incidence of individual AEs was generally similar between the droxidopa and placebo groups with the exception of nervous system disorders (13.7% vs. 7.6%, respectively) and Injury, poisoning and procedural complications (1.5% vs. 7.6%). Events with a higher incidence in the droxidopa group compared with the placebo group included headache (6.1% vs. 3.0%, respectively) and dizziness (3.8% vs. 1.5%). Events with a higher incidence in the placebo group compared with the droxidopa group included fall (6.8% vs. 0.8%, respectively) and loss of consciousness (2.3% vs. 0).

In the open label parts of the studies, events were most commonly reported in the SOC categories of nervous system disorders (22.1%), gastrointestinal disorders (10.1%) and general disorders and administration site conditions (8.8%). The most commonly reported individual AEs were headache (10.4%), dizziness (7.2%), nausea (4.5%), fatigue (4.3%), and fall (4.1%).

The sponsor did an analysis in which AE rates were adjusted by duration of exposure. In this analysis, AE rates per patient-year for the most common AEs were consistent across dose groups, with the exception of the 100 mg TID dose, which showed a higher rate for certain of the more common AEs. As shown in Table 41, headache, falls, and dizziness occurred at a relatively higher rate in the 100 mg dose group, suggesting that these adverse events are not likely to be side effects of the droxidopa and are probably more likely symptoms of the underlying disease. This analysis is reassuring and is consistent with what is known about the underlying diseases studied in this development program.

Table 41: AEs by patient-year of exposure during Studies 301 and 302

	Droxidopa											
	100 mg TID (PY=2.55) (N=444)		200 mg TID (PY=2.63) (N=405)		300 mg TID (PY=2.78) (N=359)		400 mg TID (PY=2.48) (N=285)		500 mg TID (PY=1.91) (N=224)		600 mg TID (PY=2.96) (N=174)	
	E	Rate	E	Rate	E	Rate	E	Rate	E	Rate	E	Rate
Any AEs	**121**	**47.47**	**91**	**34.55**	**86**	**30.92**	**61**	**24.59**	**61**	**31.92**	**82**	**27.68**
Headache	17	6.67	9	3.42	7	2.52	12	4.84	9	4.71	8	2.70
Dizziness	10	3.92	5	1.90	2	0.72	5	2.02	7	3.66	7	2.36
Loss of consciousness	1	0.39	0	0	1	0.36	0	0	0	0	1	0.34
Fatigue	3	1.18	5	1.90	5	1.80	4	1.61	1	0.52	2	0.68
Fall	7	2.75	5	1.90	4	1.44	0	0	2	1.05	4	1.35
Urinary tract infection	3	1.18	2	0.76	1	0.36	0	0	0	0	5	1.69

AE=adverse event; E=event; PY-patient-years; TID=three times daily
Note: Treatment-emergent AEs were included based on the study phase and treatment received prior to the onset of the event. If a patient had multiple occurrences of an AE during the same treatment phase, the patient was included only once in the respective patient count. Events were counted each time in the event (E) column. Adverse events were coded using MedDRA version 10.1. Individual study data adjusted for exposure can be found in ISS Table 2.1.2.15 and 2.1.2.16
Source: ISS Table 2.1.2.14 (Section 11.13).

Source: Table 2-17, ISS

For my own AE analysis of the double blind phase, I used the sponsor's dataset: DAE.xpt. I recategorized all the AEs in the development program using both broader and narrower categories. The most common adverse events (AEs) in the development program were fall, headache, loss of consciousness (LOC), urinary tract infection, dizziness and various musculoskeletal complaints. The most common AEs in the droxidopa group that exceeded AEs occurring on placebo by at least 2% were headache and musculoskeletal complaints. According to my analysis, falls occurred far more often on placebo than on droxidopa [10/173 (5.8%) vs. 2(1.2%), respectively]. Changes in blood pressure, both high and low, that were counted as AEs were unusual 2(1.2%) for each direction of shift and for each treatment group. It is likely that changes in blood pressure were underreported because the data were being captured elsewhere.

Table 42. Common AEs during DB phase of Study 301 and Study 302

	Droxidopa	Placebo
N	171	173
Headache	10 (5.8)	6 (3.5)
Infection	7 (4.1)	6 (3.5)
Bacterial infection	6 (3.5)	4 (2.3)
Dizziness/ wooziness	6 (3.5)	3 (1.7)
UTI/ bacturia/pyuria/ colonization	6 (3.5)	3 (1.7)
Musculoskeletal Complaints	6 (3.5)	1 (0.6)
Fatigue/ Asthenia/Weakness, fatigue,malaise	5 (2.9)	3 (1.7)
Near Syncope or syncope or fainting	4 (2.3)	5 (2.9)
LOC/ syncope/ fainting	4 (2.3)	5 (2.9)
High Blood Pressure	2 (1.2)	1 (0.6)
Low Blood Pressure	2 (1.2)	1 (0.6)
Gait disorder/psychomotor disturbance/ tremor	4 (2.3)	1 (0.6)
Nausea/Vomiting/reflux	3 (1.8)	3 (1.7)
Fall	2 (1.2)	10 (5.8)
Injury	2 (1.2)	3 (1.7)
Respiratory	2 (1.2)	2 (1.2)
Hypertension/ BP increase	2 (1.2)	1 (0.6)
Anxiety/ mood alteration/depression	2 (1.2)	1 (0.6)
Appetite Poor	2 (1.2)	1 (0.6)
Liver enzymes high	2 (1.2)	0 (0)
Hypotension	2 (1.2)	0 (0)
Cold/Sinus/cough, sore throat	2 (1.2)	0 (0)
Fever/Chills/ diaphoresis	2 (1.2)	0 (0)

One way to assess the significance of AEs when there is no placebo controlled data is to examine the relationship between the adverse event and the dose that the patient was on when the AE occurred. If the event is truly related to drug, one would expect that there would be more events on higher doses. The problem with this analysis is that the doses of the potentially offending substance, droxidopa, were titratable. The droxidopa dose may have been reduced if patients were having symptoms that might have been construed as drug related. It is possible, therefore, that the AE could have occurred after downward titration and might have been attributed to a lower patient-dose. To create Table 43, I used only AEs that occurred during the open-label parts of the studies, including the OL extension trials. The AEs were counted by patient-dose. If a patient had 2 headaches on 200 mg TID of Droxidopa, for instance, there would be 1 headache counted for that patient-dose. If a patient had a headache on 200 mg TID and a headache 600 mg TID, a headache would be counted for each patient dose (200 and 600mg TID). Since the AEs are counted per 100 patient years, the numbers are higher than what was actually seen in the program because there was much less than 100 patient years of exposure.

The slope (rightmost column in Table 43) shows the strength of the dose-response relationship for each adverse event term or group of terms. The higher the slope, the more likely there is a dose relationship, and the terms in the table are sorted by descending slope. The top row is labeled UTI/ bacturia/pyuria/ colonization. While there may be a trend of more of these events with increasing dose, the 84 events at the 0 mg dose clearly weakens the correlation. Of all the categories of AEs, this analysis is most useful when looking at falls. It appears that there are relatively fewer falls at higher doses (i.e., the slope is negative). This observation suggests that droxidopa may reduce falls at higher doses. Again, while it appears that there is no clear dose relationship by this analysis, conclusions are limited by the titration design of the studies.

Table 43: Dose related AEs (Doses are TID)

Dose	**0**	**100**	**200**	**300**	**400**	**500**	**600**	**slope**
100 Patient-years	**18**	**11**	**28**	**34**	**41**	**33**	**58**	
UTI/ bacturia/pyuria/ colonization	84	9	36	18	41	45	64	0.092
Near syncope or syncope or fainting	45	0	25	26	19	24	24	0.032
Hematuria	11	0	4	12	2	3	16	0.019
CHF, cardiomegaly, pulmonary edema	6	0	7	0	7	15	5	0.016
Worsening underlying neurol disorder	6	0	4	0	5	6	9	0.016
Fungal Infection	0	0	0	0	0	3	5	0.010
Proteinuria	0	0	0	9	2	3	5	0.008
High potassium	6	0	0	3	2	0	5	0.007
Hypertensive crisis	0	0	0	3	0	0	5	0.007
Ventricular ectopy	6	0	0	0	5	3	2	0.006
LOC/syncope/ fainting	23	19	22	21	17	21	24	0.006
Fall	62	85	33	29	22	27	28	-0.088

I did not attempt to study subgroup effects (sex, age, underlying disease, region, race, etc.) on adverse event rates because of the small numbers of patients and relatively small numbers of AEs. The sponsor did some analyses which revealed no concerning findings.

7.4.2 Laboratory Findings

In all, there were no concerning laboratory changes.

The sponsor reported that there were more patients that had shifts in lymphocytes from normal to low seen in the droxidopa-treated patients. In study 301, there was 1 (1.3%) placebo-treated patient versus 7 (8.9%) droxidopa-treated who shifted from normal to low lymphocytes and in study 302, no placebo-treated patients versus 3 (6.3%) droxidopa-treated patients had shifts from normal to low.

When looking at the End of Study distribution of absolute lymphocyte counts (using dlab.xpt), both groups included patients with low values (0.3 -1.1 X 10^9/L). There were approximately 25 patients in each of the study groups with values in this range (25 in the droxidopa group and 27 in the placebo group). For patients with values in the 0.6 or lower range, there were 3 in the droxidopa group and 2 in the placebo group. The only SAE related to leucopenia was in a patient with a history of leucopenia. I am not overly concerned about this signal.

The sponsor also reported that there were shifts in serum creatinine and BUN, more so in the droxidopa treatment group. Patients treated with droxidopa had a higher incidence of shifts to increased blood urea nitrogen (BUN) compared with placebo-treated patients (10.7% vs. 4.5%) and increased creatinine compared with placebo-treated patients (6.9% vs. 1.5%). The sponsor explained that there was no clear temporal trend in these parameters.

Nevertheless, there was a preclinical signal for renal toxicity. For this reason, I looked at the End of Study distribution of serum creatinine levels (using dlab.xpt). Both groups included patients with high values (> 1.3 mg/dL); 11 patients in the droxidopa group and 12 in the placebo group. The maximum difference in serum creatinine between randomization and end of study was 0.5 mg/dL for the droxidopa group and 0.9 mg/dL for the placebo group. 11 patients in the droxidopa group had increases of serum creatinine of 0.2 or more compared to 19 patients in the placebo group. The SAEs related to renal failure appeared to be from volume depletion in one case and urinary tract obstruction in another. Therefore, there do not appear to any concerning signals for renal safety for droxidopa.

7.4.3 Vital Signs

Since droxidopa was titrated and patients were eliminated for elevated SBP during the pivotal trials, dose relationships between droxidopa and abnormal vital signs are challenging to capture. In Table 44 I compared patients at the end of the double blind phases of Study 301 and Study 302 by vital signs. Patients in droxidopa could be on any dose of droxidopa, 100 mg tid to 600 mg tid. Placebo-treated patients were on placebo for at least 1 week and at most 2 weeks because prior to that they were in their titration phase. The most apparent difference between the two groups is the average SBP. As one would expect, there is a difference between the two groups with the droxidopa patients having an average SBP of 7.4 mmHg higher than the placebo group at end of study. Not shown in the table is that only one patient in the droxidopa group had a SBP of > 200. That patient's SBP was 214 and was treated with droxidopa 200 mg tid (see Table 45).

There were too few patients in each of the dosing groups to make any conclusions about risk for systolic hypertension by dose. In Table 45, it can be seen that there appears to be no dose relationship for SBP at end of study.

It is likely that droxidopa treated patients will occasionally have hypertensive reactions. Since SBP is easily monitored, this is not a highly concerning safety issue in most cases. However, there were 3 cases of "hypertensive crisis" in the development program (in Study 304). These patients were fortunate in that they had no permanent sequelae of these events. However, it is likely that there will be cases of hypertension related sequelae such as angina, myocardial infarction, stroke, congestive heart failure and death if droxidopa is approved.

There were no concerning changes in heart rate seen in the development program as shown in Table 44.

Table 44: Difference in SBP, DBP and HRATE at Baseline and End of Study (last visit of DB phase) between treatment groups (Study 301 and 302 combined)

	Droxidopa	Placebo
Immediatetly prior to stand up:	**n=133**	**n=136**
BL SBP average	128.7	126.6
BL SBP maximum	178	186
EOS SBP average	135.9	128.5
EOS SBP maximum	214	200
BL DBP average	76.3	76.5
BL DBP maximum	105	110
EOS DBP average	80.0	77
EOS DBP maximum	110	109
	n=83	**n=85**
BL HRATE average	69.9	70.2
BL HRATE maximum	96	109
EOS HRATE average	70.5	69.9
EOS HRATE maximum	94	92

Source: DORTHO.xpt
SBP=systolic blood pressure, DBP = diastolic blood pressure, HRATE= heart rate, BL = baseline, EOS = end of study

Table 45: SBP in mmHg (immediately prior to standing up) by dose at End of Study (last visit of DB phase) of 301 and 302 combined

		n	Average BL	Max BL	Average EOS	Max EOS
Placebo		136	126.6	186	128.5	200
Droxidopa	**100 mg tid**	8	127,8	160	133	152
Droxidopa	**200 mg tid**	18	126	178	135	214
Droxidopa	**300 mg tid**	22	134	169	138.9	187
Droxidopa	**400 mg tid**	20	129	162	135.2	172
Droxidopa	**500 mg tid**	16	123	173	127.6	166
Droxidopa	**600 mg tid**	49	129.2	172	138.3	194

Source: DORTHO.xpt
SBP=systolic blood pressure, BL = baseline

The shift table below (Table 46) demonstrates that patients with higher baseline blood pressures are more likely to have elevated SBP on droxidopa (10% if baseline SBP =161-180 mmHg vs. 0.6% if baseline SBP <145 mmHg). These data suggest that patients with baseline hypertension are more likely to have worsening hypertension and should be monitored closely for this potential adverse reaction.

Table 46: Shift Table of SBP for Study 301

Risk of Developing SBP>200: 0.6% 7.9% 10%

maximum SBP	<145	145-160	161-180	181-200	>200
>200	1	5	4	0	6
181-200	4	16	10	7	
161-180	15	24	26		
145-160	29	18			
<145	109				
	n=158	n=63	n=40	n=7	n=6

maximum screening/baseline SBP

In Study 305, the ambulatory blood pressure study, 20 patients had their blood pressure measured for 24 hours before treatment and then again at the end of Study 305. Among all subjects, there was a statistically significant increase of 7.3 mmHg (±11.72) in the 24-hour mean systolic BP (p=0.027) in subjects comparing their off vs. on-drug treatment periods. Most of these patients had been on droxidopa for several weeks by the time of the second monitoring visit (mean exposure was 44 days; (range: 31-71 days). While, there were a few exceptions, most patients had SBPs in the range of 70 to 170 mmHg for the 24-hour monitoring period.

7.4.4 Electrocardiograms (ECGs)

There were no concerning findings in the double blind or open label extension studies.

A thorough QT Study was done with an active control. The effect of droxidopa on cardiac repolarization using the QTcI interval showed no signal. No clear signal of any effect on heart rate, atrioventricular conduction, or cardiac depolarization as measured by the PR and QRS interval durations was observed. A preliminary evaluation suggests that droxidopa does not prolong QT interval. The QT Consult is pending with the Interdisciplinary Review Team for QT Studies Consultation.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

There were 7 incidents of neoplasms in the open-label safety data set: basosquamous carcinoma of the cheek, thyroid nodule, bladder cancer, lentigo maligna, benign parathyroid tumor, skin cancer and squamous cell carcinoma. It is not possible to evaluate the relationship between droxidopa and the development of these cancers.

7.6.2 Human Reproduction and Pregnancy Data

There was one pregnancy in a patient on droxidopa. This resulted in discontinuation of droxidopa. No follow up information was provided in the submission.

7.6.3 Pediatrics and Assessment of Effects on Growth

No assessment done.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

There was one case of overdose reported postmarketing in Japan. The patient ingested 7700 mg of droxidopa and experienced a hypertensive crisis that resolved promptly with treatment. If approved, there will need to be labeling regarding the potential for hypertensive crisis with overdose.

A thorough review on the possibility of abuse potential is in the process of being conducted by the Controlled Substance Staff (CSS) to determine if the drug should be scheduled. The review will also investigate the possibility that droxidopa might provide a desirable effect in addition to symptom relief that might have influenced the results of the studies.

The completion of this section is pending the completion of the CSS review.

8 Postmarket Experience

Droxidopa has been approved in Japan since 1989 for improvement of symptoms of frozen gait and orthostatic hypotension, syncope, dizziness on standing up and other autonomic disturbances in patients with Parkinson's, MSA and PAF. The daily dose is not to exceed 900 mg and should be divided into 2 or 3 doses. Titration is advised to be done by starting at 100 mg bid or tid and then to increase the dose by 100 mg/day every few days or every week. Post-marketing data have been collected in Japan since the marketing approval of droxidopa in 1989 through the conduct of post-marketing surveys, and through collection of spontaneous AEs reported by health care providers. The post-marketing surveys were conducted as part of the approval process in Japan and consisted of a retrospective survey completed for randomly selected individuals receiving droxidopa. The surveys were conducted from January 1989 through January 1995 and obtained results from a total of 1819 patients receiving droxidopa, the majority of these patients being treated for Parkinson's disease. Based on the small number of patients with MSA or FAP included in this original survey (144 patients) and an amendment to pharmaceutical law in Japan, which extended the post-marketing surveillance period to 10 years for orphan indications,

It is difficult to make safety determinations from postmarketing experience particularly when the patient population is very ill. However, there were 9 cases of neuroleptic malignant syndrome (NMS), a rare and life-threatening neurological disorder, in the Japanese postmarketing experience. This finding is particularly worrisome. The Japanese report did not attempt to provide good alternative explanations for the development of NMS in these cases. One patient was on a neuroleptic medication (haloperidol). One was on tiapride hydrochloride, an antipsychotic medication. Several patients were on levodopa which is known to be associated with NMS when its dose is reduced. There was no mention of levodopa dose reduction in the cases that were reported. 3 of the patients were not taking drugs that have been reported to be associated with NMS. It is unclear if droxidopa might cause NMS. Certainly, the existence of so many postmarketing cases is cause for some concern and may be sufficient reason to recommend against approval. There is a table in Appendix C of all patients that were reported in Japan.

The postmarketing cases of pulmonary edema, angina and myocardial infarction, while there was only 1 reported for each of these adverse events are cause for concern because it is plausible that NE increases will increase the risk of these events.

There was a case of a patient with aplastic anemia who apparently was rechallenged with droxidopa in addition to several antiparkinson agents and indeed had a recurrence.

The one case of acute renal failure was confounded by the development of pneumonia and dehydration. Concerning is the possibility that increased NE could cause renal ischemia by reducing renal blood flow.

The case of sudden death in a patient with Parkinson's disease is concerning because NE increase could conceivably increase risk of cardiac arrhythmia and death in a susceptible individual.

The next section summarizes the rest of the Japanese postmarketing survey.

Results of the Japanese Survey and Voluntary Reports

Among the adverse reactions described in the use-results survey and voluntary reports during the surveillance period, 23 events in 22 patients were classified as Grade 3 according to the "Classification of Serious Adverse Reactions of Drugs" (Notification No. 80 of Pharmaceuticals and Drugs Safety Division, Pharmaceutical Affairs Bureau, MHW, dated June 29, 1992): neuroleptic malignant syndrome (9 cases), consciousness disturbed, fulminant hepatitis (1 case and patient was only exposed to droxidopa for 2 days so thought to be not likely related to droxidopa), inappropriate ADH secretion syndrome (SIADH) (1 case), hypotensive shock associated with DIC, bradycardia and death (1 case), angina pectoris (1 case), myocardial infarction (1 case), cerebral infarction (1 case), sleep apnea (1 case), pulmonary edema (1 case), drug-associated aplastic anemia (1 case), acute renal failure (1 case), and sudden death (1 case in a patient with Parkinson's disease). Of these, 1 patient was reported to have angina pectoris in the use-results survey. 5 other patients were evaluated by their physicians as having serious adverse events: somnolence, hallucination, abdominal pressure, urinary retention, fever and plantar burning sensation.

There has been a high frequency of psychiatric adverse reactions such as hallucination and nocturnal delirium in the elderly.

From the Japanese postmarketing experience, a total of 131 patients out the 1819 (7.2%) patients surveyed reported a total of 194 AEs. As expected, this AE rate was considerably lower than the AE rate from the clinical study data; however, the AEs reported in the post-marketing survey followed a pattern similar to those obtained in clinical studies. The most frequently reported AEs collected during the first 6 years of the post-marketing survey (N=1819) were nausea/vomiting (n=27; 1.5%), hallucination (n=14, <1%), BP increased (n=13, <1%), ALT (SGPT) increased (n=10, <1%), anorexia

(n=8, <1%), and dizziness/lightheadedness (n=8, <1%). All of these AEs were expected AEs based on the precautions section of the approved label in Japan.

Priority survey questions were asked for events classified as psychiatric disorders, serious hypersensitivity reactions, serious hepatic or renal damage, blood disorders, serious cardiovascular disorders, or usage in pregnancy. The only AEs reported from these survey questions were for AEs in the Psychiatric disorders body system. These included 14 cases of hallucination and 3 cases of delusion, all occurring in patients with PD, and all of which were possibly related or related to droxidopa treatment.

One of the 194 AEs reported during the post-marketing survey was considered a serious AE (angina pectoris); this AE subsided after discontinuation of droxidopa and was considered possibly related to droxidopa treatment.

Hoping to gain insight into the concerns that have been raised during this review I looked for AEs for leucopenia, urinary system disorders and renal failure in the Japanese postmarketing data. One of the 194 AEs was leucopenia. Urinary system disorders were not commonly reported, with 2 cases of urinary incontinence, 1 case of "BUN increased", 1 case of nocturia and 1 case of urinary frequency.

Patients with chronic renal failure had a higher incidence of AEs in general, but most this was a small subgroup of patients and the AEs were most mild and resolved during continued treatment with droxidopa.

When AEs were stratified by background characteristics (age, sex, treatment environment, reasons for use, morbidity period, maximum daily dose, total dose, duration of use, concomitant drugs, and complications), the only factors that showed a significant increase in AE rates was for patients who were treated as inpatients compared with patients treated as outpatients, patients with renal complications, and patients with cerebral/neurological disorders.

Of the 194 AEs reported, 52.6% (102/194) of the AEs were reported within the first month of treatment. When AEs were analyzed by dose, there was a higher incidence of AEs occurring at doses below 600 mg/day than doses above 600 mg/day. This reverse dose trend was attributed to the higher incidence of AEs occurring in the first month of treatment while patients were having their dose titrated versus steady-state dosing once a maintenance dose had been established.

Patients included in the survey received droxidopa for up to 4 years and 9 months; a total of 502 patients in the survey received droxidopa for >1 year. There were no specific AEs attributed to long-term use of droxidopa.

9 Appendices

9.1 Literature Review/References

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9.2 Labeling Recommendations

To be addressed after further review.

9.3 Advisory Committee Meeting

On February 23, 2012, FDA's Cardiovascular and Renal Drugs Advisory Committee (CRDAC) convened to listen to presentations by the sponsor and FDA prior to discussing the application and voting.

The sponsor focused on studies 301and 302 and suggested that the success on the exploratory OHQ in study 302 should be considered to be supportive and compelling evidence for the efficacy of droxidopa. Dr. Papadopoulos's presentation focused on the OHQ and how this was not a validated endpoint and should not be used to support efficacy. My presentation focused on three major deficiencies: efficacy (only 1 adequate and well controlled successful trial) with no other compelling support for effectiveness, safety (no pure placebo-controlled data), and lack of evidence of durability of effect.

The committee voted 7-4 with 1 abstention and 1 non-vote to recommend approval of Northera (droxidopa) for the treatment of symptomatic neurogenic orthostatic hypotension in patients with primary autonomic failure (Parkinson's disease, multiple system atrophy and pure autonomic failure), dopamine beta hydroxylase deficiency and non-diabetic autonomic neuropathy. The 1 abstention and 1 vote would have gone against approval, so in fairness, the opinion of the committee was much more balanced than it appears on the surface.

A number of issues were raised and discussed:

- The validity of the OHQ instrument (this followed a presentation from SEALD in which its many limitations were discussed)
- The meager effect size in the single study that won (<1 point on the 11-point OHQ scale)
- Evidence of effectiveness - only one positive study and two studies that failed to show an effect on primary or secondary endpoints
- A post-hoc analysis of the study 302 showed an improvement on the OHQ score, generating the hypothesis for study 301. Study 301 did demonstrate that droxidopa improved the OHQ, but study 303 did not, in essence, refuting 301
- The fact that a single study could have supported approval if substantiated by a persuasive pharmacodynamic effect on BP, but the BP effect was only evident in study 301 and paradoxically reversed in study 303
- Lack of evidence of durabilty

- The largely uncontrolled nature of the safety database
- The 19 deaths; 18 on droxidopa vs. 0 in placebo vs. 1 prior to randomization
- A number of serious adverse events, half of them cardiovascular, where adrenergic stimulation may have played a causal role
- Supine HTN was common and a common cause to be not randomized. The fact that patients were not assessed when they were fully supine and simply when they had they had their head tilted up at 30 degrees made it possible that supine hypertension was underestimated.
- The spontaneous reports of neuroleptic malignant syndrome in Japan

Some members of the committee expressed significant concern about the limitations of the OHQ. Questions were raised about how FDA condoned the use of this faulty measure as the prespecified primary efficacy endpoint particularly because the endpoint was part of a Special Protocol Assessment (SPA). Dr. Temple explained that the use of PROs has been evolving and we are learning more about how to evaluate them for primary efficacy endpoints. In the end, the question about the validity of the scale didn't get much traction, particularly because Study 301 was also highly successful on the more acceptable (according to the SEALD team) endpoint of "dizziness, lightheadedness" (Item 1 of the OHSA). The failure of Study 301 to show a benefit on a global symptom inventories, Clinical Global Impressions-Severity and Clinical Global Impressions-Improvement was discussed very briefly. Some committee members seemed to be troubled by this negative finding.

There was also a long discussion of the modest mean effect size. Some committee members thought it was hard to make too much of the effect when the patients were preselected to respond to the drug. Others felt that the cumulative distribution function demonstrated that some patients benefitted quite a bit. At the far left part of the curve where benefits were greatest (in Study 301), there was a greater separation between drug and placebo. This amounted to ~15% of patients who were in the range of largest effect (> -3). One member reminded the committee that only 60% of the patients who enrolled were randomized because the others didn't qualify or had AEs or hypertension. This means that if Study 301 is representative of what would happen in the "real world", only 60% X 15% (9.0%) would be expected to have these great responses.

The paucity of evidence of effectiveness with the development program producing only one positive study was discussed. All agreed that study 301 was successful on its primary OHQ endpoint. The applicant tried to make the case that study 302, which showed a nominally statistically significant improvement on a post-hoc analysis of the OHQ but failed to show an effect on its primary endpoint, "supported" study 301. Most of the members of the committee rejected this concept, noting that 302 generated the hypothesis tested in 301, and can't really be considered as a supportive study. The views on study 303 weren't consistent. The applicant suggested that 303 *would have been positive*, if only the randomized withdrawal phase had been longer – long enough for the drug effect to wane. The committee recognized that this was speculation. A

somewhat more conservative interpretation was that the study simply failed to show that the treatment effect persists for more that 1 week, without casting doubt on the efficacy through 1 week. The most conservative view, expressed by perhaps a third of the committee, was that the failure of 303 undermined the credibility of 301. One committee member thought that there would not have been enough proof of efficacy if there were other treatments for symptomatic NOH. He thought that since there were no good available alternatives, the evidence in support of droxidopa's effectiveness would have to suffice.

In terms of durability of effect, one member was not concerned about absence of proof of durability of effect – believing that Study 301 was more reflective of an effect and that 303 simply was not powered well enough to show it. Other members thought that durability was not demonstrated and that this was a weakness that could be resolved with post-marketing studies.

On safety, the committee was mixed. The absence of a "pure" control group was raised and several of the committee members felt uncomfortable with not having much reliable safety data, particularly because the efficacy data was not as robust as one would like to see. Most of these committee members were very concerned about the serious adverse events. One member was concerned about the cases of neuroleptic malignant syndrome. One member was very concerned about supine hypertension and how the design of the studies precluded an adequate assessment of it. A few members were very concerned about the effects NE would have on patients who have underlying cardiovascular disease. However, over half of the members seemed to accept that pure autonomic failure carries a poor prognosis and that many patients die of various complications. These members did not share as much concern about the possibility that droxidopa could have worsened patients' outcomes. One of the committee members felt that the Japanese spontaneous reports of neuroleptic malignant syndrome should be discounted because of stimulated reporting, poor quality and confounding of many reports, and regional differences in the practice of medicine.

In the end, the vote wasn't really 7 to 4, but 7 to 6. One member who most certainly would have voted "no" did not vote. One committee member abstained, but his logic was consistent with a "no" vote. The "yes" votes seemed to be based on the logic that NOH is a severely debilitating disease with no good therapies, and droxidopa appeared to improve symptoms in at least some patients. They also seemed to have the impression that some people benefit greatly from the drug – mostly from the patient testimonials because this could not be known from the data. Some committee members specifically mentioned that the patient testimonials were important in swaying their opinions. Members voting for approval seemed to be in favor of a post-marketing study to establish the drug's durability of effect. The "no" voters cited concerns about the limited strength of evidence of efficacy and lack of evidence of efficacy beyond 1 week, a particular concern for a therapy for a chronic disease. They also expressed concerns for safety in patient populations with cardiovascular disease, likely to be present in patients with NOH because of their usually advanced age.

9.4 Appendix A

The PGLO (same as CGI-I, patient) is the scale used to measure improvement by the patient, the CGLO (same as CGI-I, clinician) is the scale used to measure improvement by the Investigator and the PGLOBL (same as CGI-S, patient) is the scale used to measure severity by the patient. The CGLOBL (same as CGI-S, clinician), the scale to measure severity by the Investigator is not included in this section but presumably resembles the CGLOBL.

Clinical Global Impressions-Patient (PGLO)

1. Was assessment performed? — List: YES_NO

**2. Reason not performed:

Severity of Illness

**3. How severe is your Orthostatic Hypotension (OH) at this time? — List: SEVERE

Global Improvement ? Rate total improvement regardless as to whether or not you believe it is due entirely to drug treatment.

Compared to your condition at your Baseline Visit 2, how much has your orthostatic hypotension changed?

**4. Select — List: IMPROVE

** Conditional Question

List:YES_NO

Label	Value
[Blank]	
No	0
Yes	1

List:SEVERE

Label	Value
[Blank]	
Not assessed	0
Normal, no OH	1
Borderline OH	2
Mild OH	3
Moderate OH	4
Marked OH	5
Severe OH	6
Among those patients most extremely ill with OH	7

List:IMPROVE

Label	Value
[Blank]	
Not Assessed	0
Very much improved	1
Much improved	2
Slightly improved	3
No change	4
Slightly worse	5
Much worse	6
Very much worse	7

Clinical Global Impressions-Clinician (CGLO)

1. Was assessment performed?	List: YES_NO
**2. Reason not performed:	

Considering your total clinical experience with this particular population, how severe is the patient?s orthostatic hypotension (OH) at this time?

**3. Severity of Illness	List: SEVERE

Global Improvement ? Rate total improvement regardless as to whether or not you believe it is due entirely to drug treatment.

Compared to the patient?s Baseline Visit 2 condition, how much has his/her orthostatic hypotension changed?

**4. Global Improvement	List: IMPROVE

** Conditional Question

List:YES_NO

Label	Value
[Blank]	
No	0
Yes	1

List:SEVERE

Label	Value
[Blank]	
Not assessed	0
Normal, no OH	1
Borderline OH	2
Mild OH	3
Moderate OH	4
Marked OH	5
Severe OH	6
Among those patients most extremely ill with OH	7

List:IMPROVE

Label	Value
[Blank]	
Not Assessed	0
Very much improved	1
Much improved	2
Slightly improved	3
No change	4
Slightly worse	5
Much worse	6
Very much worse	7

Clinical Global Impressions-Patient-Baseline (PGLOBL)

1. Was assessment performed?	List: YES_NO
**2. Reason not performed:	
Severity of Illness	
**3. How severe is your Orthostatic Hypotension (OH) at this time?	List: SEVERE

** Conditional Question

List:YES_NO

Label	Value
[Blank]	
No	0
Yes	1

List:SEVERE

Label	Value
[Blank]	
Not assessed	0
Normal, no OH	1
Borderline OH	2
Mild OH	3
Moderate OH	4
Marked OH	5
Severe OH	6
Among those patients most extremely ill with OH	7

9.5 Appendix B

SERIOUS ADVERSE EVENTS

STUDY 301

1. 80 year old female with PD had SAEs of nausea and vomiting, both moderate in severity. The patient was hospitalized with a presyncopal event and the SAEs resolved within 1 day. The patient was discontinued from the drug.

2. 49 y/o male with MSA had SAEs of urinary tract infection, ureteric obstruction, and neurogenic bladder. All 3 events started during the follow-up period, 3 days after the last dose of droxidopa treatment. The patient was hospitalized and the SAEs resolved within 13 days

STUDY 302

3. 77 year old male with PD, had an SAE of coronary artery disease (diagnosed with an anterior septal and inferior myocardial infarction on the Screening ECG) that was moderate in intensity. The patient was hospitalized and treated by cardiac catheterization and two drug-eluting stents. The study drug was discontinued on the day after starting study drug as a result of the SAE. The event did not resolve during the reporting period.

4. 86 y/o male with PAF, had SAEs of cardiac failure congestive (moderate intensity) and pneumonia (severe intensity). The event of pneumonia resulted in discontinuation of study drug. The patient was hospitalized as a result of these events. Both events resolved after 1 month.

5. 73 year old female with PD, had an SAE of orthostatic hypotension (dizziness and feeling faint were her symptoms) that was moderate in intensity. The patient was hospitalized as a result of the SAE. The event occurred 6 days after the last dose of study drug and resolved after 1 month.

6. 58 y/o female with MSA had an SAE of leucopenia that was severe in intensity. Patient was taking trimethoprim prophylactically (labeled to be associated with leucopenia) and had a 2-year history of leucopenia. The trimethoprim treatment was discontinued and her neutrophil count improved. The study drug was continued throughout the duration of the event. The event resolved after 6 days.

Double-Blind Phase SAEs – Placebo Group

7. 84 y/o female with PD, had SAEs of mental status changes and urinary tract infection; both were moderate in intensity. She was on placebo at the time of these events. The patient was hospitalized; the mental status was resolved within 3 days and the urinary tract infection was resolved within 17 days. Study drug was continued throughout the duration of the event.

8. 70 y/o female with MSA and h/o depression who was on droxidopa 600 mg TID and developed severe depression that resulted in hospitalization.

9. 58 y/o female with MSA who was on droxidopa 600 mg tid and experienced syncope while trying to move from her wheelchair. She was apparently unresponsive for 20 minutes. The patient had a history of syncope. She was not entered into the randomized phase of study 303.

10. 74 y/o female with NDAN. The patient was on droxidopa 600 mg tid. She developed headache leading to hospitalization. Droxidopa was discontinued and then restarted. After restarting droxidopa, the headaches returned and then she started having syncope. She then was switched from droxidopa to midodrine

which resulted in worsening syncope. She received IV fluids and the event resolved.

11. 66 y/o female with MSA. Patient had a h/o chronic inflammation of her urinary tract and hypertension. She was on droxidopa 200 mg tid of droxidopa. She developed severe renal failure which was attributed to hydronephrosis due to ureteral stenosis.

12. 62 y/o male with MSA. Patient was on droxidopa 600 mg tid. He developed DVT. Droxidopa was not discontinued but the patient's AE was not resolved at the time of the report.

13. 68 y/o female with PD on droxidopa 100 mg tid. The patient had a history of anxiety and palpitations. She developed visual hallucinations. Study drug was discontinued.

14. 66y/o male with h/o PD. The patient was on droxidopa 600 mg tid. He developed hallucinations and confusion and was hospitalized. After discontinuation of droxidopa, the symptoms improved. The patient was not rechallenged.

15. 86 y/o male with PD on droxidopa 200 mg tid. The patient had a GI bleed with bright red blood passage per rectum. The diagnosis was a diverticular bleed. Following this event which resolved spontaneously, the patient experienced a fall and fractured C2 and T2.

16. 86 y/o female with MDA on droxidopa 200 mg tid. Patient fell and was hospitalized. Droxidopa was tapered up to 400 mg tid and her fludrocortisone dose was increased. She also received a 3 L normal saline infusion

17. 83 y/o female with PD on droxidopa 200 mg tid. Patient was generally deteriorating while on study drug with multiple falls and hip pain. She had a positive Methoxyisobutyl Isonitrile stress test during an evaluation of her cardiac risk for hip replacement surgery. She underwent cardiac catheterization and was found to have stable coronary disease. She then had a hip replacement. The patient developed pneumonia which was considered an SAE. She then developed hypertension that resulted in the discontinuation of study drug.

18. 73 y/o male with PD on droxidopa 100 mg tid at time of the event. Patient was admitted for wheezing, weakness and general deterioration from Parkinson's and dementia. He developed hemorrhagic bronchitis. His situation improved and he was discharged form the hospital.

19. 72 y/o male with PD on droxidopa 500 mg tid. The patient fell and experienced an intertrochanteric fracture of the left hip. After a brief hiatus, droxidopa was restarted.

20. 74 y/o male with PAF on droxidopa 400 mg tid. The patient was diagnosed with well-differentiated squamous cell carcinoma of the skin in two locations; left wrist and left forearm.

21. 60 y/o male with PAF on droxidopa 500 mg tid. The patient had an elective cardiac catheterization with a successful stent replacement and the placement of an additional (new) stent for progressive angina due to coronary artery disease. The patient was kept overnight for observation and reported a decrease in angina symptoms. Several months later the patient developed convulsive syncope, probably from worsening of his underlying orthostatic hypotension.

22. 55 y/o male with MSA on droxidopa 600 mg tid. The patient had a syncopal episode with loss of consciousness, a fall and a nose fracture.

23. 81 y/o male with PD on droxidopa 300 mg tid. Patient had a fall and a hip injury that was not a fracture. He had a syncopal episode in the emergency room and was hospitalized overnight only.

24. 85 y/o female with PD on droxidopa 200 mg tid at the time of event. She developed new onset atrial fibrillation with a rate of 82 bpm. The event resolved despite staying on droxidopa.

25. 65 y/o male with NDAN on droxidopa 600 mg tid at the time of the event. He developed fever, paralysis of the extremities and was diagnosed in the hospital with acute encephalopathy secondary to urinary tract infection and renal insufficiency. The renal insufficiency apparently resolved with volume resuscitation. At a later date he developed respiratory difficulty and was admitted for failure to thrive. It seems that his condition had generally worsened and he was admitted to hospice. This all occurred within a couple of months of starting drug.

26. 73 y/o male with NDAN on droxidopa 400 mg tid at the time of event. He was admitted with a large DVT of the right LE and then developed hyponatremia and volume depletion.

27. 75 y/o male with PAF on droxidopa 100 mg tid at the time of the event. The patient developed unstable angina and required a new stent.

STUDY 304

28. 75 y/o female with PAH on droxidopa 300 mg tid. She developed pyelonephritis and was treated successfully with IV antibiotics. Study drug was temporarily discontinued and then restarted.

29. 77 y/o male with PAF on droxidopa 600 mg tid who developed hypertensive crisis on day 104 of taking drug. The event resolved after discontinuation of droxidopa.

30. 70 y/o male with MSA on droxidopa 600 mg tid who developed hypertensive crisis on day 105 of taking drug. The event resolved after discontinuation of droxidopa.

9.6 Appendix C

Table 47: Profile of Patients with Neuroleptic Malignant Syndrome

		1	2	3	4
Primary disease		Parkinson's disease Alzheimer's disease	Parkinson's disease	Striatonigral degeneration	Spinocerebellar degeneration
Severity of primary disease		Moderate	Moderate		Severe
Sex		M	F	F	M
Age at onset		71 y	69 y	51 y	54 y
Time of onset		May 31, 1991	November 24, 1991 (1st) February 12, 1992 (2nd)	December 12, 1992	July 26, 1993
Medication status	Onset of symptoms	Day 5 after treatment initiation	1st: Day 3 after dose titration [2nd: Day 7 after dose titration]	Day 4 after reduction of dose	Day 4 after reduction of dose
	Daily dose at onset	100 mg	1st: 1,200 mg [2nd: 1,200 mg]	1,100 mg	600 mg
Symptoms	Fever (max temp)	37° level	39°	39°	38-39°
	Muscle rigidity	Intense	No increase	Increased	Increased
	Consciousness disturbed	Unconscious Twilight state	Delirium	Consciousness decreased (Drowsy)	Mild Stupor
	CPK value (max)	2950	7442	886	1161
Concomitant drugs (S = suspected drug)	Levodopa preparation	O(S)	O(S)	O	O(S)
	Amantadine hydrochloride	O	O(S)	O	
	Bromocriptine mesilate		O (at 2nd)		O
	Other main drugs (S)	Haloperidol (S)	Tiapride hydrochloride (S)		
	No. of drugs (total)	7	7	3	3
Evaluation by reporting physician of causal relationship with DOPS		Unknown	Unknown	Possible	Unknown

Table 48 (continue): Profile of Patients with Neuroleptic Malignant Syndrome

		5	6	7	8	9
Primary disease		Multiple system degeneration	Parkinson's disease	Shy-Drager syndrome	Shy-Drager syndrome	Parkinson's disease
Severity of primary disease			Severe	Severe	Severe	Severe
Sex		M	M	M	M	F
Age at onset		79 y	69 y	65 y	51 y	70 y
Time of onset		January 7, 1994	ca. June 24, 1994	July 2, 1994	July 8, 1994	August 16, 1994
Medication status	Onset of symptoms	Continuing	Continuing	Continuing	Day 1 after titrating dose	Continuing
	Daily dose at onset	300 mg	400 mg	300 mg	1,200 mg	300 mg
Symptoms	Fever (max temp)	37°	Above 40°	42°	39.5°	40.6°
	Muscle rigidity	Intense		Moderate - Severe	None	Unknown
	Consciousness disturbed	Coma	Transient decrease to pre-onset consciousness level	Coma	None	Yes
	CPK value (max)	1200 level	2001	9756	2682	1388
Concomitant drugs (S = suspected drug)	Levodopa preparation		O (S)			O (S)
	Amantadine hydrochloride		O (S)		O	O (S)
	Bromocriptine mesilate		O (S)			
	Other main drugs (S)					
	No. of drugs (total)	2	8	3	8	9
Evaluation by reporting physician of causal relationship with DOPS		Possible	Possible	Possible	Possible	Possible

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/s/

MELANIE J BLANK

03/18/2012

This review supersedes my previous NDA review. It provides a description of the advisory committee, corrects some factual errors and an updated executive summary.

CLINICAL REVIEW

Application Type	NDA
Submission Number	203202
Submission Code	Sequence 0048
Letter Date	8/13/2013
Stamp Date	8/13/2013
PDUFA Goal Date	2/13/2014
Reviewer Name	Shari L. Targum, M.D.
Review Completion Date	12/5/2013
Established Name	L-DOPS (droxidopa)
(Proposed) Trade Name	NOTHERA™
Therapeutic Class	Sympathomimetic
Applicant	Chelsea Therapeutics
Priority Designation	P
Formulation	oral capsules
Dosing Regimen	TID
Indication	Treatment of Symptomatic Neurogenic Orthostatic Hypotension (NOH)
Intended Population	Patients with Primary Autonomic Failure (Parkinson's disease [PD], Multiple System Atrophy [MSA], Pure Autonomic Failure [PAF]), Dopamine Beta Hydroxylase (DBH) deficiency, or Non-Diabetic Autonomic Neuropathy (NDAN)

Table of Contents

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

This reviewer recommends a Complete Response action for droxidopa in the treatment of symptomatic neurogenic orthostatic hypotension (NOH), because of inadequate evidence of effectiveness.

1.2 Risk Benefit Assessment

In the original application (9/28/2011), studies 301, 302 and 303 were submitted to support effectiveness and, despite randomizing "enriched" populations of responders, only study 301 met its primary endpoint, the composite OHQ, as well as OHSA item-1 scores. While the Agency was concerned about the lack of consistency with failed studies 302 and 303, the Agency nonetheless considered study 301 as a single study to support effectiveness. However, the reviewers' confidence in study 301 was undermined by the highly positive and unusually homogenous pattern of results in a single site (Table 1 and Figure 2), along with this site's disproportionate contribution to the overall positive results. The Agency subsequently issued a Complete Response Action (3/28/2012).

The applicant submitted a dispute resolution request, which was denied; however, the applicant was informed that Study 306B "has the potential to serve as the basis for a resubmission of the NDA in response to the…request for at least one additional adequate and well-controlled trial….Given the significant limitations of the data from Study 301…to support a finding of substantial evidence of effectiveness, it will be important that the results of Study 306B be strongly positive; i.e., the trial should closely adhere to the criteria specified in the Agency's effectiveness guidance for a single trial…." (Dr. Jenkins: Dispute resolution letter, 2/28/2013).

In this resubmission, the applicant has provided study 306B as an additional pivotal efficacy study. Study 306B began as an amendment to study 306 after an unblinded interim analysis; study 306 met criteria for futility, with an original primary endpoint of the change in OHQ from baseline to Week 8. Study 306 was amended to studies 306A and 306B; 306B retained the same study design and population as the original study 306, but amended the primary endpoint to patient-reported falls, and later amended the primary endpoint to OHSA item-1 from baseline to Week 1 (thus, the primary endpoint for 306 was changed twice). Study 306B met its amended primary endpoint, OHSA item-1 from baseline to Week 1, with an effect size of -0.94 (p value =0.028) on an 11-point scale (see section 9.2). Other Week 1 endpoints, such as OHQ, clinician and patient-reported CGI-I and CGI-S, and standing systolic blood pressure (SBP), trended in a consistent direction (i.e., favorable for droxidopa) (see Table 19, first column, with an elevation in the lowest standing SBP [0-3 minutes] and favorable reductions in all scores).

It is difficult to judge whether the integrity of study 306B was affected by the unblinded interim analysis, along with access by contract research organization statisticians to the treatment codes. The primary endpoint and SBP effects appear reduced after the access to treatment codes was revoked (Table 22). However, if we give the applicant the benefit of the doubt, and consider study 306B to support efficacy, the results do not meet the criteria as a "robust" or "strongly positive" single study to support a symptom benefit (see Presubmission Regulatory Activity, section 2.5). This conclusion is based on the small treatment effect, exceeded by the 3-fold higher intra-subject variability. In addition, more patients on droxidopa (vs. placebo) discontinued prior to the first post-randomization OHSA-item 1 (even if patients discontinuing from 306A are counted in discontinuations in 306B), presenting a dilemma in how to interpret the missing OHSA item-1 data.

It is also not clear how to interpret the apparent imbalance in concomitant fludrocortisone use (at or following baseline) by droxidopa patients vs. those on placebo; while this imbalance did not appear to have a large influence on the primary endpoint (Table 18), this imbalance could suggest differences between treatment groups not captured by the usual baseline characteristics, but potentially affecting comparability.

The results of study 306B, along with results of study 303, support a lack of effect durability in this chronic condition. Study 306B met its primary endpoint at Week 1 after dose titration; however, by Week 2, the next time point, OHSA item-1 results for droxidopa and placebo appeared to merge together (Figure 8). Results for study 303, where responders received 3 months of open-label droxidopa therapy followed by a randomized, double-blind 2-week withdrawal, showed no significant difference between groups in the primary endpoint (OHQ) or OHSA item-1 and lower standing SBP for droxidopa compared to placebo.

The most common adverse events in study 306 and in the original application were a higher incidence of hypertension, headache, nausea and dizziness in droxidopa-treated patients compared to placebo (Tables 27, 28; also see prior Clinical Review); in study 306 there was also a higher incidence of insomnia and abnormal dreams (Table 13). While the updated safety database contains more placebo-controlled and long-term experience, there remains limited long-term exposure at the highest doses and no long-term controlled studies.

A total of 27 deaths occurred across the applicant's clinical studies, of which 16 deaths were reported in the original NDA, one reported in the 90-Day Safety Update and 10 newly reported deaths in the long-term uncontrolled study 304 (one reviewed in the original clinical review and nine in this review). There were no deaths in study 306. Cardiovascular serious events can occur spontaneously in the elderly or in high-risk patients and it is difficult to calculate the attributable risk without a comparator group. However, since ABPM data demonstrated that droxidopa increases mean systolic and diastolic BP, one can plausibly expect an increase in stroke and cardiovascular risk; should droxidopa be approved, its use should be discouraged in patients with high cardiovascular risk.

Also discussed at the previous advisory committee meeting were spontaneous post-marketing reports of neuroleptic malignant syndrome (NMS) reported from Japan. The applicant

subsequently submitted a total of 29 cases which were reviewed by two neurologists; each concluded that most of the cases did not meet the two criteria for NMS. There were no clearly defined cases of NMS in study 306. However, one publication cited NMS as "a rare entity and often not recognized…the reported incidence rates vary between 0.02 and 2.44%, though 0.2% has been the most frequently cited figure over the past decade."[1] It is possible that the safety database in the applicant's development program is not large enough to exclude these rare events.

In summary, the applicant submitted 4 studies (301, 302, 303 and 306) in the droxidopa application; two of these studies, 301 and 306B, met their primary endpoint. Although studies 301, 302 and 303 were enriched populations (e.g., enrolling responders), studies 302 and 303, both randomized withdrawal studies, failed to meet their respective primary endpoints, and 306A (not enriched, but with a primary endpoint measured at Week 8) met the criteria for futility. Of the two studies (301, 306B) that succeeded in meeting their amended primary endpoints, one site with unusually homogeneous positive results (507) contributed disproportionately to the positive result (301); the other study (306B), created after an unblinded interim analysis, met its amended primary endpoint with a statistically significant treatment effect at a single early time point. Additional issues affecting the interpretability of study 306B results include: the imbalance in premature discontinuations and missing data (more in the droxidopa-treated group); the small treatment effect in the face of larger intra-subject and inter-subject variability; lack of durability beyond the Week 1 time point; and the inconsistent OHQ, OHSA item-1 and standing SBP curves between study 306A and 306B. Collectively, these concerns undermine this reviewer's confidence in study 306B as a "strongly positive" trial supporting a benefit with droxidopa.

1.3 Recommendations for Postmarketing Risk Management Activities

None.

1.4 Recommendations for other Post Marketing Study Commitments

None.

1 Anath J et. al. Neuroleptic malignant syndrome: risk factors, pathophysiology, and treatment. *Acta Neuropsychiatrica 2004: 16: 219-228.*

2 Introduction and Regulatory Background

2.1 Product Information

Droxidopa is a synthetic amino acid analog that is converted to norepinephrine by the enzyme dopa decarboxylase, the same enzyme that metabolizes levodopa to dopamine. Other than an additional beta-hydroxyl group, droxidopa is structurally identical to levodopa, a catecholamine pro-drug used for augmentation of dopamine. The conversion of droxidopa to norepinephrine (NE) can occur peripherally or centrally.
If symptomatic NOH results from inadequate release or utilization of NE from sympathetic vasomotor neurons, droxidopa treatment is thought to increase central and peripheral levels of NE, increasing blood pressure (BP). However, the exact mechanism of action of droxidopa is not known. In humans, droxidopa treatment results in a transient increase in serum levels of NE; it is possible (though not supported by available data) that NE is rapidly taken up by tissues
.
According to the clinical pharmacology reviewer, data from 306B showed no clear dose dependent effect of droxidopa on SBP.

2.2 Tables of Currently Available Treatments for Proposed Indications

Midodrine is the only other approved treatment for symptomatic neurogenic orthostatic hypotension (NOH). Midodrine is a prodrug that is converted to desglymidodrine, an alpha-1 receptor agonist. Midodrine received accelerated approval in 1996 on the basis of an increase in standing SBP, a surrogate endpoint reasonably likely to predict clinical benefit; however, subsequent clinical trials have not shown that midodrine improves symptoms.

A variety of nonpharmacologic approaches have been employed to treat symptoms of NOH, including:
1. Getting up slowly;
2. Elevating the head of the bed;
3. Wearing elastic stockings.

Unapproved pharmacologic agents include:
1. Fludrocortisone;
2. Desmopressin;
3. Dihydroergotamine;
4. Indomethacin;
5. Erythropoietin.

2.3 Availability of Proposed Active Ingredient in the United States

Droxidopa is not approved in the United States and is only available for experimental purposes.

2.4 Important Safety Issues with Consideration to Related Drugs

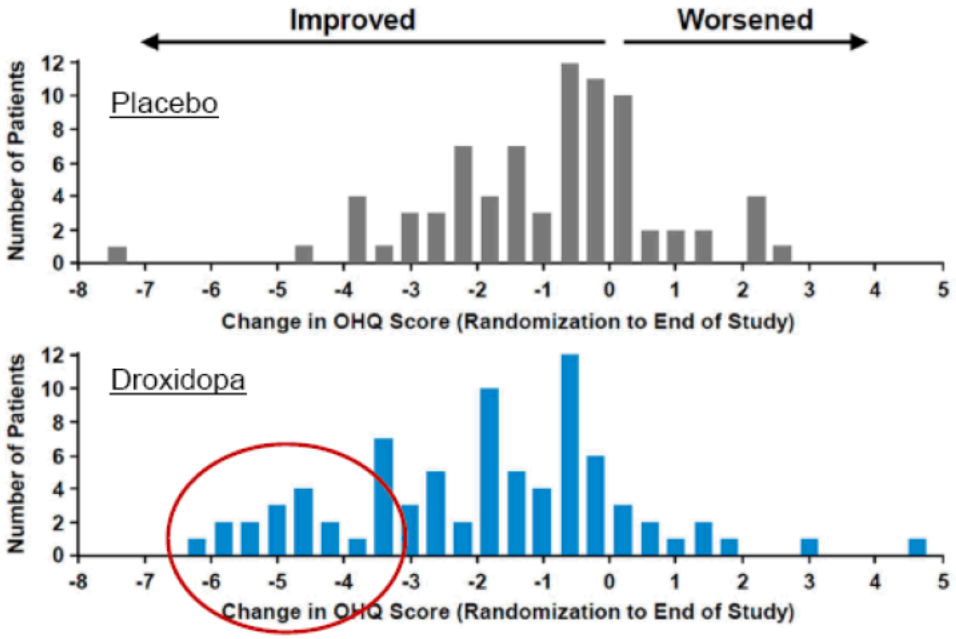
Intravenous NE is used to increase BP in shock; in patients with intact autonomic activity, compensatory vagal reflex activity slows the heart. Peripheral vascular resistance increases in most vascular beds, and renal, splanchnic, and hepatic blood flow are reduced.
Adverse effects of intravenous norepinephrine include hypertension; aggravation of tissue ischemia, resulting in gangrene; anxiety, restlessness, tremor and headache.

Droxidopa bears a structural similarity to levodopa, an immediate precursor to dopamine and used as part of dopamine replacement therapy in Parkinson's disease. Levodopa can enter the brain, whereas dopamine is blocked by the blood-brain barrier. To prevent formation of dopamine in the peripheral tissues, levodopa is commonly administered with a peripheral dopa decarboxylase inhibitor such as carbidopa. Adverse effects (or complications) of levodopa therapy include: the "wearing off" effect and dyskinesias; in addition, it is not considered safe to discontinue levodopa suddenly as such action can induce the malignant neuroleptic syndrome, characterized by fever, sweating, rigidity, mental confusion and obtundation (source: Hazzard's Geriatric Medicine and Gerontology).

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The original New Drug Application was submitted on September 28, 2011 and discussed at an Advisory Committee meeting on February 23, 2012. Of the three clinical trials submitted (301, 302, 303), only one (301) met its primary endpoint, change in the Orthostatic Hypotension Questionnaire score (OHQ) after 7 days of treatment.

Figure 1. Study 301: Histogram of Responses for the Primary Endpoint: OHQ Score (presented at the Advisory Committee, 2012).



After NDA 203202 was discussed at the advisory committee, the review team further analyzed study 301, noting that 6 out of the 15 "super responders" (patients experiencing ≥ 4 point reduction in OHQ score) were enrolled in site 507 (n=16) in the Ukraine.

Table 1. Study 301: Primary endpoint: overall and excluding site 507.

	OHQ		
	randomization	end of study	change
All Sites			
Droxidopa N = 82	5.10	3.30	-1.81
Placebo N = 80	4.99	4.07	-0.92
treatment effect			-0.89
p-value			0.003
Omit Site 507			
Droxidopa N = 73	4.98	3.49	-1.49
Placebo N = 73	4.84	3.91	-0.93
treatment effect			-0.56
nominal p-value			0.07
Site 507 Only			
Droxidopa N = 9	6.07	1.70	-4.37
Placebo N = 7	6.51	5.75	-0.76
treatment effect			-3.61
nominal p-value			0.000000005

(Source: Dr. Unger; Office Director Decisional Memo, 3/28/2012).

When site 507 was removed from the analysis, the results were no longer statistically significant.

The Agency statistical reviewer conducted a simulation of 10,000 runs to randomly remove 16 subjects (9 droxidopa, 7 placebos from the study 301 dataset; the Agency statistical reviewer found that the probability of observing a p-value of 0.082 or greater by randomly removing 16 subjects by the ITT population was less than 0.0001.

The reviewers also observed an unusual pattern of homogeneity in site 507 given the large placebo effects and amount of variability observed elsewhere.

Figure 5: End-of-Study OHQ, OHSA Item 1, CGI-I, and Standing Systolic BP at Site 507

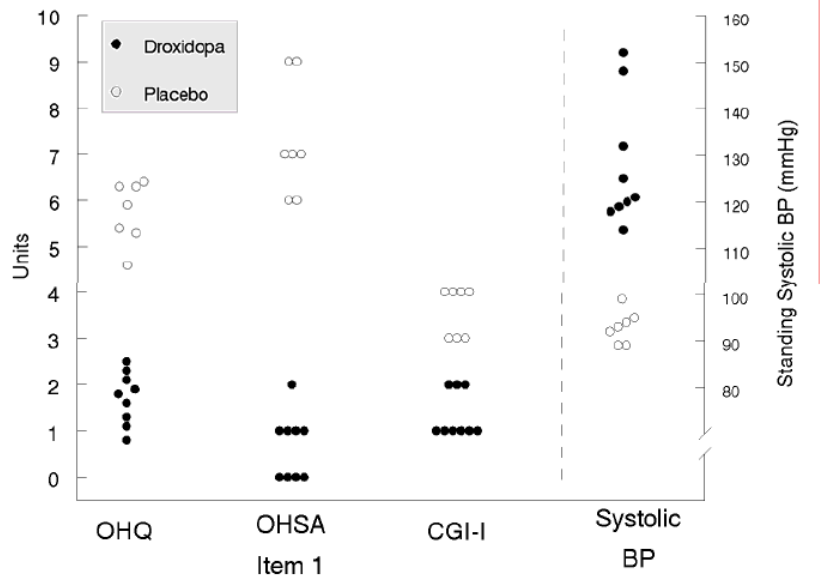


Figure 2. End-of-study endpoints at site 507 (source: Dr. Unger; Office Director Decisional Memo, 3/28/2012).

The Agency inspected 3 sites in the Ukraine (sites 505, 507 and 513) and found minor violations not thought to rise to a level that would influence data integrity, study outcome, or subject safety.

According to FDA guidance, a single, large, multicenter, adequate and well-controlled study can support effectiveness under certain circumstances. However, "if analysis shows that a single site is largely responsible for the effect, the credibility of a multicenter study is diminished."[2] Moreover, the inconsistency of the overall findings, including the results of studies 302 and 303, undercut the positive findings in study 301. A complete response letter was therefore issued on March 28, 2012, stating that an additional positive study would be needed. The Agency recommended that the applicant design a study demonstrating durability of effect over a 2- to 3-month period.

On December 12, 2012, the applicant filed a formal dispute resolution request, appealing the requirement to conduct an additional clinical trial for approval. The applicant argued that the Agency treated droxidopa differently compared to the way it treated midrodrine. Midodrine was approved in 1996 under the accelerated approval provision based on improvement in standing systolic blood pressure, a surrogate endpoint considered reasonably likely to predict clinical benefit in patients with orthostatic hypotension. The applicant for droxidopa requested either

2 Food and Drug Administration. Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products.

accelerated approval or full approval with a post-approval clinical trial to confirm clinical benefit in patients with NOH.

The applicant also proposed that the results of Study 306B, which was ongoing at the time of the original application, be accepted as support for approval of droxidopa. Study 306B was a randomized, 8-week, placebo-controlled trial of droxidopa in patients with Parkinson's disease and symptomatic orthostatic hypotension. The applicant also proposed to change the primary endpoint of the ongoing trial from reduction in the rate of falls to OHSA item 1.

While denying the sponsor's appeal, the Agency believed that study 306B, a relatively large trial in patients with NOH, could form the basis for an NDA resubmission in response to the request for at least one additional adequate and well-controlled trial. The Agency had reservations concerning the usefulness of Study 306B, based on concerns related to the unblinded interim analysis of Study 306A (the first part of Study 306), and the possibility that decisions about the conduct and analysis of the trial were based on knowledge of ongoing trial data. The Agency also stated that, "Given the significant limitations of the data from Study 301… to support a finding of substantial evidence of effectiveness, it will be important that the results of Study 306B be strongly positive; i.e., the trial should closely adhere to the criteria specified in the Agency's effectiveness guidance for a single trial" (February 28, 2013 letter from Dr. Jenkins).

2.6 Other Relevant Background Information

Droxidopa has been approved in Japan since 1989 for orthostatic hypotension, syncope, and dizziness on standing up in Familial Amyloid Polyneuropathy and Shy-Drager Syndrome (i.e., MSA) and for the treatment of freezing phenomenon and dizziness on standing up in PD. In 2000, this approval was expanded to include the alleviation of vertigo, staggering, dizziness on standing up, lassitude, and weakness in hemodialysis patients with OH.

The approved maintenance doses in Japan are 300 mg-600 mg daily, not to exceed 900 mg/day, lower than the maximum doses proposed in the United States.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The overall submission appears to be of acceptable quality. An outstanding issue is whether the integrity of study 306B was affected by the unblinded interim analysis of study 306 and the access of PPD statisticians to randomization codes for all study subjects.

3.2 Compliance with Good Clinical Practices

The applicant appears to have complied with Good Clinical Practices; however, final reports of study 306B site inspections are pending.

3.3 Financial Disclosures

From the available financial disclosures, [redacted] received the largest amount of consulting fees. [redacted] received a total of $197,400, including consulting fees of $186,400.00 and honoraria of $11,000.00. [redacted]

[redacted] According to the financial disclosure statement, [redacted] received $128,400, including consulting fees of $117,400.00 and honoraria of $11,000.00 [redacted]

[redacted] received a total of $121,212.00, including [redacted] in study grants; consulting fees of $37,932; and honoraria of $22,000.00.

[redacted] received consulting fees in the amount of $35,864.00. [redacted] and received a total of $29,500.00, including consulting fees of $17,000.00 and honoraria of $12,500.00.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls (CMC)

The CMC reviewer for Northera ™ droxidopa capsules, 100 mg and 200 mg, has recommended approval, pending the overall Office of Compliance (OC) recommendation. Based on the drug product stability data, the CMC reviewer has recommended 48 month expiration dating period for droxidopa 100 mg and 200 mg capsules manufactured using the [redacted] synthesis

method at Dainippon Sumitomo Pharma facility, and packaged in 90counts/90 cc HDPE bottles, 21 count/60 cc bottles, and 9 count/40 cc bottles. The expiration date of 36 months for 100 mg and 200 mg Northera ™ capsules packaged in aluminum foil blister packs was granted previously. The expiration period for 300 capsules is not granted due to the insufficient amount of stability data for granting expiry.

4.2 Clinical Microbiology

Not applicable to this submission.

4.3 Preclinical Pharmacology/Toxicology

There is no new preclinical pharmacology/toxicology information.

4.4 Clinical Pharmacology

The clinical pharmacology review is pending at this time.

5 Sources of Clinical Data

The main sources of clinical data are the clinical studies provided by the applicant and postmarketing information.

5.1 Tables of Clinical Studies

Table 2. Table of the sponsor's clinical studies

Name	Total N	Design	Double-blind treatment	Primary endpoint	Result
306B	174	Double-blind, placebo-controlled, parallel-group	8-10 weeks	OHSA item 1	Met primary endpoint; study prematurely terminated
306A	51	Double-blind, placebo-controlled, parallel-group	8-10 weeks	OHQ composite	Met criteria for futility.
301	162	Double-blind, placebo-controlled, parallel-group induction design	1 week	OHQ composite	Met primary endpoint
302	101	Double-blind, placebo-controlled, randomized withdrawal	2 weeks	OHSA item 1	Failed to meet primary endpoint
303	75	Open-label extension to 301 and 302 (randomized double-blind withdrawal)	2 weeks	OHQ composite	Failed to meet primary endpoint
304	350	Open-label extension	N/A	Safety	
305	18	24-hour ABPM substudy of 301 (after 1 mo. treatment)	Substudy of 301 and 304	Safety	↑ 24 hour mean SBP and DBP

5.2 Review Strategy

This review focused on 306B but also referred to prior reviews of studies 301, 302, 303 and 304.

5.3 Discussion of Individual Studies

The designs of studies 301, 302 and 303 are shown in Figure 3. The design of study 306 is shown in Figure 4.

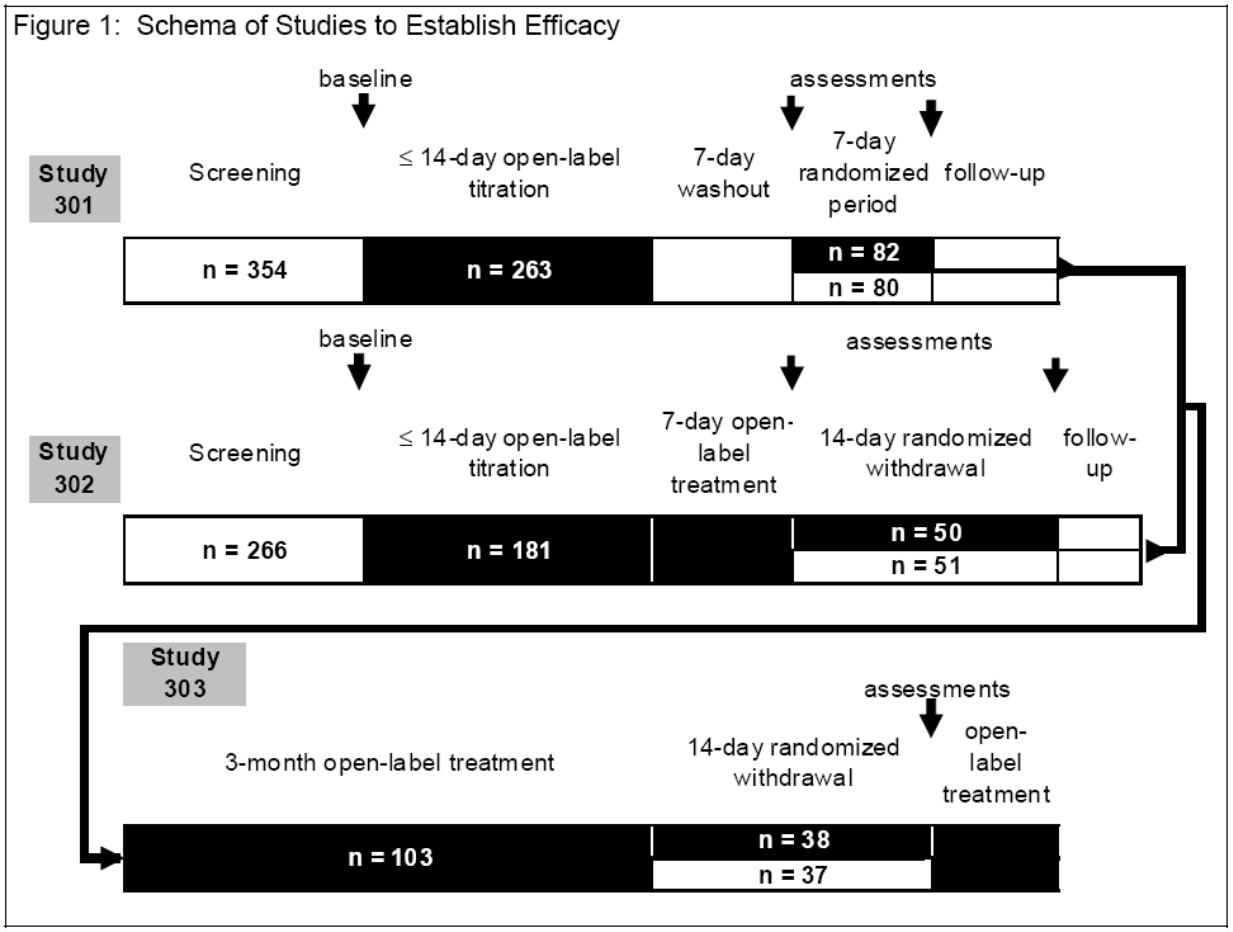


Figure 3. Study Design: studies 301, 302, 303 (source: Dr. Unger, Office Director decisional memo, 3/28/2012).

In the original submission, the applicant presented 3 studies to support efficacy. Importantly, all 3 included enrichment designs. The two main studies (301 and 302) included an open-label titration period; potential subjects had to tolerate the drug and be categorized as a "responder" (based on symptom and BP response) before they could be enrolled in the placebo-controlled phase of the study. The third study (303) enrolled subjects who had been enrolled in 301 and 302. Thus, by definition, the subjects in 303 had been responders as well.

Study 302 had a 2-week titration phase, where all subjects received escalating doses of droxidopa. Doses were increased on the basis of symptom and BP response, as well as tolerability. As noted above, subjects who tolerated droxidopa and appeared to have a symptom response were enrolled in the randomized portion of the study. These subjects (about 60% of the total number treated) received 1 additional week of droxidopa, followed by a 2-week randomized double-blind withdrawal. This study failed (p=0.5) on its 1° endpoint (dizziness), but won on a post-hoc analysis of a 10-factor symptom and symptom-impact scale, the Orthostatic Hypotension Questionnaire (OHQ).

With the post-hoc "win" on the OHQ in study 302, and with a similar trial ongoing and still blinded (study 301), the applicant changed the 1° endpoint of 301 to OHQ, with concurrence of the Division. That study ultimately won on the OHQ endpoint. However, a single site, 507, contributed disproportionately to the positive result and undermined the Agency's confidence in the results of 301.

A third smaller study (303) enrolled subjects who had completed study 302. All subjects were treated with droxidopa for 3 months, followed by a 2-week randomized withdrawal phase. Had the study "won," it would have substantiated the results of study 301 and shown durability of the treatment effect for 3 months; however, the study did not win on the OHQ 1° endpoint – it did not even show a trend. Of note, only half of the original number of subjects remained in the study after 1 year. The applicant hypothesized that study 303 failed because the effects of the drug persist beyond 2 weeks.

Studies 301, 302 and 303 are reviewed in detail in the clinical review of the original submission (Dr. Blank, Clinical review, 1/27/2012). The study design for 306 can be found in Figure 4. Study 306B is reviewed in detail in section 9.1.

In contrast to the other clinical studies, the design for 306 randomized patients to placebo and droxidopa without a prior enrichment. In addition, 306 employed a longer double-blind treatment period than the other clinical studies, affording an opportunity to evaluate durability.

6 Review of Efficacy

Efficacy Summary

6.1 Indication

The sponsor has proposed droxidopa for chronic use to treat symptomatic neurogenic orthostatic hypotension. The proposed dose range is 100 to 600 mg TID.

6.1.1 Methods

As this is a resubmission, this review will include a detailed discussion of study 306B and summaries of studies 301, 302 and 303. The reader is referred to the primary medical review of the original NDA submission for a detailed discussion of 301, 302 and 303.

6.1.2 Demographics:

All studies enrolled adult patients with NOH. The original NDA submission enrolled patients with NOH associated with primary autonomic failure (Parkinson's disease [PD], multiple system atrophy [MSA], or pure autonomic failure [PAF]), dopamine beta hydroxylase deficiency (DBHD) or non-diabetic autonomic neuropathy (NDAN). Study 306 enrolled patients with PD and used sites in the United States. Patients with diabetes and those with significant cardiac, renal and hepatic diseases were excluded.

Baseline characteristics for 301, 302, 303 and 306B are displayed below. The most common underlying disease was Parkinson's disease. Study 306B had the highest mean age, the highest SBP (calculated in 306B as the lowest SBP in the first 3 minutes) and the lowest baseline OHSA item-1 score.

Table 3. Baseline characteristics: studies 301, 302, 303 and 306B

	301		302		303		306B	
	Placebo (PBO) N=81	Droxidopa N=81	PBO N=51	Droxidopa N=50	PBO N=37	Droxidopa N=38	PBO N= 82	Droxidopa N= 89
Male [n (%)]	43 (53)	41 (51)	32 (63)	30 (60)	24 (65)	23 (61)	52 (63)	62 (70)
White [n (%)]	76 (94)	81 (100)	48 (94)	49 (98)	35 (95)	37 (97)	79 (96)	85 (96)
Black [n (%)]	1 (1)	0	0	0	0	0	1 (1)	2 (2)
Parkinson's [n (%)]	31 (38)	35 (43)	23 (45)	21 (42)	18 (49)	20 (53)	82 (100)	89 (100)
MSA [n (%)]	12 (15)	14 (17)	13 (26)	17 (34)	9 (24)	8 (21)	--	--
PAF [n (%)]	28 (35)	26 (32)	10 (20)	8 (16)	7 (19)	8 (21)	--	--
DBH [n (%)]	0	0	1 (2)	0	0	1 (3)	--	--
NDAN [n (%)]	6 (7)	2 (3)	3 (6)	2 (4)	2 (5)	0	--	--
Other [n (%)]	4 (5)	4 (5)	1 (2)	2 (4)	1 (3)	1 (3)	--	--
Mean age (SD)	56 (20)	57 (17)	67 (11)	63 (14)	66 (12)	68 (13)	72 (8)	73 (8)
US [n (%)]	33 (41)	32 (40)	32 (63)	25 (50)	22 (60)	24 (63)	82 (100)	89 (100)
OHQ mean (SD)	5.6 (2.0)	6 (1.7)	6.0 (2.2)	6.2 (1.9)	6.3 (1.9)	6.4 (1.8)	5.7 (1.6)	5.5 (1.5)
Mean SBP standing +3 min (mm Hg) (SD)	90.7 (16.8)	90.8 (15.6)	88.0 (19.0)	87.0 (17.6)	89.8 (19.8)	89.4 (15.2)	95.7 (20.1)	94.7 (21.5)
Mean OHSA-1 (SD)	5.4 (2.9)	5.4 (2.5)	6.3 (2.3)	6.6 (2.0)	6.7 (2.1)	6.5 (1.6)	5.1 (2.3)	5.1 (2.0)

6.1.3 Patient Disposition

A total of 62% and 56% of enrolled patients met the selection criteria and were enrolled in the double-blind period in Studies 301 and 302, respectively. There were few discontinuations from the short double-blind phase (Table 5), with the most common reason being treatment failure.

Patient discontinuations from study 306B can be found in Table 17.

Table 4. Patient enrollment in Studies 301 and 302

Study	Number Enrolled	Number enrolled in DB
301	263 (101 OL only)	81 placebo 81 Droxidopa
302	181 (80 OL only)	51 placebo 50 Droxidopa

(Source: Clinical review, original submission, 1/27/2012)

Table 5. Patient disposition in Studies 301 and 302

	OL Phase	DB Phase	
		Placebo N=135	Droxidopa N=134
Total Patients Treated	181		
All Patients Randomized		135	134
Patients randomized and treated in DB phase		131 (97.0)	132 (98.5)
Completed Study Per Protocol		119	125
Completed DB Phase (> 6 days for 301 and > 11 days for 302)		121 (89.6)	131 (99.2)
Reason for Discontinuation (from Per Protocol)			
Treatment Failure	107 (58.6)	6 (50)	1 (14.2)
Adverse Event	25 (13.8)	2 (16.7)	1 (14.2)
Protocol Violation	9 (5.0)	3 (25)	3 (42.9)
Withdrew consent	11 (6.1)	0	
No symptoms	1 (0.6)	0	
Noncompliance	1 (0.6)	0	1 (14.2)
Misunderstanding	0	1 (8.3)	1 (14.2)
Investigator Decision	2 (1.1)	0	
Randomization limit/ Sponsor decision	15 (8.3)	0 0	
Titration failure	2 (1.1)	0	
Missing*	5 (2.8)	0	
High BP	1(0.6)	0	

* (study 301) site considered them complete but they were not considered to be complete

(Source: Clinical review, original submission, 1/27/2012)

6.1.4 Analysis of Primary Endpoint(s)

The primary endpoints of the efficacy studies are displayed in Table 6. The reviewers of the original submission evaluated the various questionnaires; the Study Endpoints and Labeling Development reviewer felt that the OHSA item-1 captured the most important symptoms of the patients with symptomatic orthostatic hypotension.

Table 6. Droxidopa efficacy studies: Summary of primary endpoints and treatment effects

Study	Primary endpoint	Treatment effect	p-value
301	OHQ	-0.9	0.003
302	OHSA item-1	-0.6	0.5
303	OHQ	-0.3	0.4
306B	OHSA item-1	-0.9	0.028

(Sources: Dr. Stockbridge, Divisional memo, 3/15/2012; Table 19).

For a detailed analysis of the other endpoints in 306B, please see Section 9.1.

In addition, the reader is referred to the reviews of the previous submission for a detailed discussion of the OHQ and OHSA item-1 questionnaires.

7 Review of Safety

Safety Summary

7.1 Methods

This review updates the safety review from the original submission, using used the clinical trial data (301, 302, 303, 304 and 306), available literature, and the postmarketing data from Japan.

The sponsor has integrated safety data from studies 303 and 304 into a long-terms study grouping.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

In the original NDA application, the total patient exposure in the Chelsea program was 752 patients, with 276 patients exposed for at least 6 weeks and 64 exposed to the maximum dose of 600 mg TID; only 93 patients were exposed to droxidopa for at least one year and, of those exposed, only 26 were exposed at the maximum dose of 600 mg TID.

In this update, a total of 920 subjects (820 patients in Phase 2/3 trials and 120 healthy volunteers) were exposed to droxidopa in the Chelsea and European DSP-sponsored studies.
Of the 820 patients exposed to droxidopa, 573 patients were exposed for at least 6 weeks and 111 exposed to the maximum dose (600 mg TID). A total of 263 patients were exposed to droxidopa for at least one year, of which 57 were exposed to the maximum dose. While there is more exposure to droxidopa than in the original application, there remains limited information concerning long-term (e.g., $\geq$ 1 year) exposure to high doses of droxidopa.

Table 7. Patient exposure in the sponsor's and European DSP-sponsored Phase 2/3 clinical program:

Table 1-3 Estimates of Patient Exposure

	Duration of Exposure to Droxidopa					
	<6 weeks	≥6 weeks	≥3 months	≥6 months	≥1 year	≥2 years
Total Daily Dose (mg):						
200	28	27	27	25	25	0
300	80	25	16	10	6	2
400	24	21	17	13	9	2
600	151	99	67	56	38	9
900	178	115	100	89	52	24
1200	155	96	85	70	38	15
1500	93	81	64	47	38	16
1800	111	109	100	81	57	24
Total Number of Patients	**820**	**573**	**476**	**391**	**263**	**92**

Subjects enrolled in Studies 101, 102, 20/1859-94, and 20/1860-94 are not counted in this table.
Source: ISS V1 Table 1.2.2.4 (Section 11.13) and ISS V2 Table 20.1 (Section 11.11).

A total of 638 patients were exposed to droxidopa (doses 300-1800 mg/day) in studies 301, 302, 303, 304 and 306. One can observe limited long-term exposure to the highest doses.

Table 8. Patient exposure by dose in Studies 301, 302, 303, 304 and 306.

Table 1-4 Summary of Patient Exposure to Droxidopa by Dose in Chelsea-Sponsored Studies

	Droxidopa Average Total Daily TID Dose[1]						
	300 mg (N=56)	600 mg (N=95)	900 mg (N=128)	1200 mg (N=155)	1500 mg (N=93)	1800 mg (N=111)	Total (N=638)
Categorical Duration of Treatment, n (%)							
<6 weeks	56 (100.0)	95 (100.0)	128 (100.0)	155 (100.0)	93 (100.0)	111 (100.0)	638 (100.0)
≥6 weeks	11 (19.6)	59 (62.1)	81 (63.3)	96 (61.9)	81 (87.1)	109 (98.2)	437 (68.5)
≥3 months	8 (14.3)	41 (43.2)	70 (54.7)	85 (54.8)	64 (68.8)	100 (90.1)	368 (57.7)
≥6 months	5 (8.9)	34 (35.8)	65 (50.8)	70 (45.2)	47 (50.5)	81 (73.0)	302 (47.3)
≥1 year	4 (7.1)	22 (23.2)	30 (23.4)	38 (24.5)	38 (40.9)	57 (51.4)	189 (29.6)
≥2 years	2 (3.6)	4 (4.2)	8 (6.3)	15 (9.7)	16 (17.2)	24 (21.6)	69 (10.8)

1. Total duration of treatment was tabulated based on the average daily dose of droxidopa received during Studies 301, 302, 303, 304, and/or 306A and 306B.
Source: ISS V2 Table 20.1 (Section 11.11).

Considering the rarity of "orphan disease" status, this exposure seems reasonable. However, it is possible that this drug, if approved, would be used "off-label" in a broader population.

In addition to the exposure shown above, a total of 1255 subjects were exposed to droxidopa 100-1200 mg/day (maximum exposure 2 years) in registration studies for approval in Japan. Postmarketing surveys collected data in an additional 1856 patients (not clear if overlap existed with patients in registration studies).

Exposure for patients in study 306 is summarized below:

Table 9. Exposure in Study 306 (safety set)

Table 1-5 Summary of Exposure in Study 306 - All Patients (Safety Set)

	Placebo (N=108)	Droxidopa (N=114)
Last Titration Dose, n (%)		
100 mg	7 (6.5)	9 (7.9)
200 mg	8 (7.4)	11 (9.6)
300 mg	18 (16.7)	18 (15.8)
400 mg	8 (7.4)	24 (21.1)
500 mg	15 (13.9)	8 (7.0)
600 mg	52 (48.1)	44 (38.6)
Duration of Exposure in Titration Period (days)		
n	108	114
Mean (SD)	10.4 (4.00)	10.4 (4.08)
Median	10.0	10.0
Min, Max	2, 23	1, 20
Duration of Exposure at Stable Dose [1] (days)		
n	108	114
Mean (SD)	52.7 (16.48)	46.1 (22.01)
Median	58.0	57.0
Min, Max	2, 78	2, 71
Duration of Exposure Overall [2] (days)		
n	108	114
Mean (SD)	60.2 (17.55)	54.0 (23.12)
Median	65.5	64.0
Min, Max	2, 79	2, 78

One can observe a longer mean duration of exposure (both overall and at stable dose) in the placebo group compared to those treated with droxidopa.

7.2.2 Explorations for Dose Response

The phase 3 studies involved dose titration to effect or lack of tolerability, making it difficult to explore dose response.

7.2.3 Special Animal and/or In Vitro Testing:

In this resubmission, there were no new special animal/in vitro testing.

7.2.4 Routine Clinical Testing

As in the original program, supine blood pressure measurements were made when subjects were 30 degree elevated from the supine position.

7.2.5 Metabolic, Clearance, and Interaction Workup:

There were no studies specifically targeted toward metabolism, clearance or drug interactions. The most common concomitant medication in study 306 was Sinemet. Theoretically, carbidopa can interfere with the conversion of droxidopa to norepinephrine, affecting efficacy of droxidopa. In addition, droxidopa could also decrease the effectiveness of levodopa. However, a subgroup analysis of patients in 306B analyzed by concomitant Sinemet use did not reveal an obvious treatment interaction.

7.3 Major Safety Results

Most patients enrolled in the long-term extension studies had a primary diagnosis of Parkinson's disease (63%); about 19% of patients were diagnosed with PAF and 13% with MSA. The mean age of patients in studies 303 and 304 was 65 years; the majority were male (60%) and While (96%) and enrolled in the U.S. (69%).

7.3.1 Deaths

There were no deaths reported in Study 306.

There were a total of 16 deaths in the Chelsea-sponsored studies (6 occurring within the reporting period, within 7 days of discontinuation of droxidopa therapy, and 10 occurring outside the reporting period); these events were reviewed by Dr. Blank in the original clinical review. In addition, there were 17 deaths in the DSP-sponsored European studies (also reviewed by Dr. Blank) (and 2 deaths in the clinical studies in Japan).

Two deaths, submitted after the original NDA application, were reviewed by Dr. Blank.

Nine additional deaths in study 304 are reviewed below:

Table 10. NDA resubmission: additional deaths in study 304:

Study	Patient ID	Age/Gender	Study Day	Droxidopa dose	Event
304	113003A	62/W/M/PAF	550	600 mg TID	Cardiac arrest (coded as MI): found unresponsive; history of coronary artery disease/MI/stent.
304	113006A	53/W/M/MSA	777	600 mg TID	Progression of MSA; died at home.
304	116002	61/W/F/PD	1032	600 mg TID	Died in sleep.

304	116009	73/W/M/MSA	814	600 mg TID	Subdural hemorrhage
304	126009	79/W/M/PD	737	600 mg TID	Aspiration of food; respiratory arrest
304	132023Z	83/W/F/PD	189 (d/c 110 days before fatal AE)	400 mg TID	Fell at home, fractured humerus and femur; respiratory distress in rehabilitation facility, leading to pulseless electrical activity (CXR suggested aspiration), death due to respiratory failure.
304	146001A	85/W/M/PD	549	600 mg TID	Pulmonary infection, followed 1 week later by fatal respiratory arrest.
304	146004A	83/W/F/PD	530	600 mg TID	3 episodes of falling with hip fractures; cardiac arrest during third hospital admission.
304	168004A	62/W/M/PD	477 (d/c 23 days before fatal AE)	600 mg TID	Increased syncope and falls; urosepsis/possible aspiration/dehydration/acute kidney injury; hydrated and given antibiotics; then expired due to cardiopulmonary arrest the next day.

Note: Patients from study 306 were distinguished with Z; patients from 303 were distinguished with A.

The applicant also identified 2 patients who died while receiving droxidopa during controlled clinical studies in patients with intradialytic hypotension in Japan. Both of these patients had diabetes; one patient died due to sepsis related to severe gangrene; the other patient with a history of cerebral hemorrhage died due to cerebral hemorrhage.

Without a comparator group, it is difficult to interpret a relationship of droxidopa to these fatal adverse events or whether these events are a consequence of the underlying disease/comorbidities and unrelated to droxidopa. However, it is possible that droxidopa may have caused or exacerbated hypertension, a known risk factor for stroke and MI.

7.3.2 Nonfatal Serious Adverse Events

There were no nonfatal serious adverse events (SAE) in droxidopa-treated patients during the short randomized, double-blind periods of placebo-controlled trials 301, 302, 303 and 304. As reported in the original NDA submission, six (1.4%) droxidopa-treated patients reported 10 SAEs in the open-label titration phase of these studies; three patients discontinued study drug due to SAEs (nausea and vomiting; coronary artery disease; and pneumonia, respectively).

There were no SAE in study 306A. In study 306B, five droxidopa patients reported 9 SAEs and four placebo patients reported 5 SAEs (Table 26). Three SAEs (atrial fibrillation in patient #110006; mental status changes in patient 156007; and hypertension in patient #184003) led to discontinuation of droxidopa. Two patients on placebo experienced syncope.

In the long-term studies, 105 of 422 patients (25%) reported 224 SAE, of which > 55% did not lead to a change in study drug; about 20% led to study drug discontinuation and 27 events (12%)

resulted in death. The most commonly reported SAE were syncope (14 patients, 3%) pneumonia (9 patients, 2%), dehydration (8 patients, 2%), hip fracture (6 patients, 1%), fall and urinary tract infection (5 patients each (1%). Syncope, pneumonia, sepsis and hip fracture were the most commonly reported SAE in the original NDA. These SAE and their incidence are difficult to interpret without a comparator. The sponsor additionally compared exposure-adjusted rates of the most common SAE (e.g., syncope, pneumonia, hip fracture) and found no increase between the original and updated analyses.

7.3.3 Dropouts and/or Discontinuations

In study 301, 13 patients (5%) in the open-label phase developed AEs that led to study discontinuation. The most common such AE was nausea (4 patients), followed by hypertension (3 patients).

In study 302, 13 (7%) patients in the open-label phase and 2 (4%) placebo-treated patients in the double-blind phase had AEs that led to study discontinuation. In the open-label phase, the most common AE reported by more than 1 patient was dizziness (3 patients).

In study 306A, one 76 year-old female (#156006) on droxidopa 200 mg TID developed abdominal heaviness, worsening blurred vision, worsening dizziness and headache (Study Day 9); two days later, the patient was found to have gallstones and a benign bladder lesion. She was discontinued due to "Other" category ("Patient and PI felt it would be best for her to stop study drug due to all the problems the patient was having.").

In study 306B, there were more premature discontinuations in droxidopa-treated patients compared to placebo-treated patients (Table 17). The most common AE leading to discontinuation was "hypertension" or "blood pressure increased" (5 out of 10 droxidopa patients discontinuing due to AE, 2 patients on placebo), followed by hallucination, abnormal dreams or mental status changes (1 each on droxidopa, or 3 patients if these AEs are "lumped"). Since there were more discontinuations in droxidopa-treated patients compared to those on placebo, one can speculate that there were additional side effects/tolerability issues. A review of the case report forms showed several instances where adverse events were temporally related to when the patients withdrew from the study (Table 30).

7.3.4 Significant Adverse Events:

In study 306, there were more hypertension or "blood pressure elevated" events in droxidopa-treated patients compared to those on placebo.

Table 11. Blood pressure-related adverse events in Study 306 (safety set)

Table 2-31 Summary of Blood Pressure-Related TEAEs in Study 306 (Safety Set)

Preferred Term	AEs n (%)	AEs E	SAEs n (%)	SAEs E	AEs Leading to Discontinuation n (%)	AEs Leading to Discontinuation E
Droxidopa-treated Patients (N=114)						
Total BP-related TEAEs	**13 (11.4)**	**21**	**1 (0.9)**	**1**	**5 (4.4)**	**5**
Hypertension	8 (7.0)	11	1 (0.9)	1	3 (2.6)	3
Blood pressure increased	4 (3.5)	9	0	0	2 (1.8)	2
Blood pressure systolic increased	1 (0.9)	1	0	0	0	0
Placebo-treated Patients (N=108)						
Total BP-related TEAEs	**9 (8.3)**	**10**	**0**	**0**	**2 (1.9)**	**2**
Hypertension	1 (0.9)	2	0	0	1 (0.9)	1
Blood pressure increased	7 (6.5)	7	0	0	1 (0.9)	1
Blood pressure systolic increased	1 (0.9)	1	0	0	0	0

AE=adverse event; BP=Blood pressure; E=event; MedDRA=Medical Dictionary for Regulatory Activities; SAE=serious adverse event; TEAE=Treatment-emergent adverse event.
Note: Treatment-emergent AEs were included based on the study phase and treatment received prior to the onset of the event. If a patient had multiple occurrences of a TEAE during the same treatment phase, the patient was included only once in the respective patient count. Events were counted each time in the event (E) column. Adverse events were coded using MedDRA version 13.0.
Source: ISS V2 Table 4.8 and ISS V2 Table 8.7.6.2 (Section 11.11): Module 5. Study 306B CSR Listing 16.4.32.

Hypertension-related events also occurred in the uncontrolled long-term extension:

Table 12. Blood pressure-related events in the long-term extension group (safety set)

Table 2-32 Summary of Blood Pressure-Related TEAEs in the Long-term Extension Study Grouping (Safety Set)

	Total Droxidopa (N=422)					
Preferred Term	TEAEs n (%)	TEAEs E	SAEs n (%)	SAEs E	AEs Leading to Discontinuation n (%)	AEs Leading to Discontinuation E
Total BP-related TEAEs	**31 (7.3)**	**36**	**6 (1.4)**	**6**	**6 (1.4)**	**6**
Blood pressure increased	7 (1.7)	8	0	0	1 (0.2)	1
Hypertension	19 (4.5)	23	2 (0.5)	2	2 (0.5)	2
Hypertensive crisis	3 (0.7)	3	2 (0.5)	2	2 (0.5)	2
Malignant hypertension	1 (0.2)	1	1 (0.2)	1	1 (0.2)	1
Blood pressure fluctuation	1 (0.2)	1	1 (0.2)	1	0	0

AE=adverse event; BP=Blood pressure; E=event; MedDRA=Medical Dictionary for Regulatory Activities; SAE=serious adverse event; TEAE=Treatment-emergent adverse event.
Note: Treatment-emergent AEs were included. If a patient had multiple occurrences of an AE during the same treatment phase, the patient was included only once in the respective patient count. Events were counted each time in the event (E) column. Adverse events were coded using MedDRA version 10.1.
Source: ISS V2 Table 2.2.2.1, Table 2.2.3, and Table 2.2.5 (Section 11.11).

Cardiovascular serious adverse events and deaths were reviewed (Table 10; Table 26); these events occurred in the elderly (e.g., > 65 year-old patients); in patients under 65 with cardiac risk factors or a prior cardiac history (e.g., history of coronary heart disease); or patients under 65 years with MSA. Except for cases of hypertension or malignant hypertension, it is difficult to interpret a relationship to droxidopa because events can also occur spontaneously in these populations.

Neurologic and psychiatric AEs:

In study 306, the incidence of headache and dizziness was higher in droxidopa-treated patients compared to placebo. In addition, there was a higher incidence of insomnia and abnormal dreams in droxidopa-treated patients.

Table 13. Study 306: Neurological AE (safety set)

Preferred term	TEAE (n, %)		SAE (n, %)		TEAE leading to discontinuation (n, %)	
	Placebo (N=108)	Droxidopa (N=114)	Placebo (N=108)	Droxidopa (N=114)	Placebo (N=108)	Droxidopa (N=114)
All neurological	**27 (25%)**	**40 (35%)**	**2 (2%)**	**1 (1%)**	**1 (1%)**	**2 (2%)**
Headache	8 (7%)	15 (13%)	0	0	0	1 (1%)
Dizziness	5 (5%)	11 (10%)	0	0	0	1 (1%)
Parkinson's disease	2 (2%)	4 (4%)	0	0	0	1 (1%)
All psychiatric	**9 (8%)**	**16 (14%)**	**0**	**1 (1%)**	**0**	**3 (3%)**
Insomnia	2 (2%)	5 (4%)	0	0	0	0
Abnormal dreams	0	2 (2%)	0	0	0	1 (1%)

Only AE with incidence $\geq$ 2% in droxidopa group were included

The long-term extension results were consistent, with headache and dizziness among the most common AE.

Table 14. Long-term extension grouping: Summary of neurologic and psychiatric AE

Preferred term	Total droxidopa (N=422)		
	TEAE n (%)	SAE n (%)	TEAE leading to discontinuation n (%)
Nervous system disorders	190 (45%)	32 (7%)	14 (3%)
Headache	56 (13%)	1 (0.2%)	1 (0.2%)
Syncope	53 (13%)	14 (3%)	1 (0.2%)
Dizziness	42 (10%)	0	1 (0.2%)

Tremor	17 (4%)	0	0
Parkinson's disease	15 (4%)	2 (0.5%)	0
Balance disorder	12 (3)	0	1 (0.2%)
Psychiatric disorders	80 (19)	12 (3)	7 (2)
Depression	20 (5)	2 (0.5)	0
Hallucination	18 (4)	3 (0.7)	2 (0.5)
Insomnia	17 (4)	0	0
Anxiety	16 (4)	1 (0.2)	1 (0.2)
Confusional state	16 (4)	1 (0.2)	0

(Only TEAE with Incidence >3% were included) (safety set)

Cerebrovascular AE:
From study 304, three cases were reviewed:
1. Cerebrovascular accident: 112002Z, 68 year-old White female with PD, hypothyroidism, type 2 DM and NOH, on 4 months of droxidopa 400 mg TID, developed leg weakness, off balance gait, difficulty swallowing and slurred speech; head CT did not reveal bleed/abnormality and she was diagnosed with freezing due to PD. MRI post-discharge revealed diffusion-positive acute parietal infarct.

2. Transient ischemic attack: 1220022Z, 75 year-old Black male with PD on droxidopa 600 mg TID, also history of dyslipidemia, orthostatic hypotension, first-degree AV block and ventricular ectopy, developed transient ischemic attack.

3. Cerebral infarct: 163004Z: 79 year-old White female with PD, on droxidopa 600 mg TID for 19 months, developed stroke (acute ischemic infarct on MRI).

7.4 Supportive Safety Results

7.4.1 Common Adverse Events:

In a placebo-controlled trial in the applicant's fibromyalgia development program, there was an increased incidence in nausea and diarrhea in droxidopa monotherapy patients vs. those on placebo.

Table 15. Study FMS-201 placebo-controlled fibromyalgia Study FMS-201:

Preferred term	Droxidopa/carbidopa combined N=64	Droxidopa monotherapy N=24	Placebo N=15
All adverse events	55 (86)	21 (88)	12 (80)

Diarrhea	8 (13)	5 (21)	2 (13)
Nausea	11 (17)	4 (17)	1 (7)
Headache	18 (28)	7 (29)	4 (27)
Palpitations	4 (6)	1 (4)	0
Cough	4 (6)	2 (8)	0
Pruritis	6 (9)	2 (8)	1 (7)
Insomnia	3 (5)	2 (8)	1 (7)
Dizziness	6 (9)	1 (4)	1 (7)

Events affecting more than 2 patients (N > 2) in droxidopa monotherapy or droxidopa/carbidopa were included.

In addition, 5 patients (6%) on droxidopa (1 patient on droxidopa monotherapy and 4 patients on droxidopa/carbidopa combination) and 0 placebo patients reported palpitations.

7.4.2 Laboratory Findings:

In study 306B, increases in serum sodium and total neutrophil count were observed in droxidopa-treated patients compared to placebo; however, these shifts were not observed in other droxidopa studies.

7.4.3 Vital Signs:

The available data do not suggest meaningful effects on heart rate.

7.4.4 Electrocardiograms (ECGs):

With the caveat of missing ECG data in study 306B, the available results do not suggest short-term ECG changes. ECGs were not conducted in Study 304.

8 Postmarketing Experience

8.1. Neuroleptic malignant syndrome:

Nine cases of neuroleptic malignant syndrome (NMS) from the Japanese postmarketing experience were reviewed by Dr. Blank in the original NDA submission. In a February 15, 2012 submission, total of 29 postmarketing cases of neuroleptic malignant syndrome in Japan, obtained from postmarketing surveillance, were submitted to the Agency. The sponsor obtained two experts in neurology to review these cases. One (Dr. Stewart Factor) stated that 20 cases did not meet the two sets of diagnostic criteria for NMS (DSM IV and Levenson); 5 met both sets of criteria and 3 met Levenson only. "None of the cases were clearly related to the drug dose escalation or withdrawal."

Dr. Agnes Nemet reviewed 28 of 29 cases (where data were available), noting that the majority of cases (17) were reported in the 1990s; and that in recent clinical trials, patient were treated with doses up to 1800 mg/day with no symptoms suggestive of NMS. In addition, 16 out of 25

events with known onset date occurred during summer months. She concluded that, although an association between droxidopa and NMS or NMS-like symptoms "cannot be entirely ruled out, the majority of reported cases either do not meet the current diagnostic criteria or have other triggering or precipitating factors explaining their occurrence."

9 Appendices

9.1 Study 306B:

Title: A Multi-Center, Double-blind, Randomized, Parallel-group, Placebo-controlled Study to Assess the Clinical Effect of Droxidopa in the Treatment of Symptomatic Neurogenic Orthostatic Hypotension in Patients with Parkinson's disease

First patient first visit June 23, 2010- last patient last visit October 23, 2012 (*Note: The protocol for 306B was dated May 12, 2011. Please see below for changes to study 306B.). 306B report date: June 13, 2013, updated July 31, 2013.*

For study 306A: first patient first visit: June 15, 2010; last patient last visit: December 14, 2010. 306A report date: December 18, 2012.

Study Centers: A total of 57 U.S. centers enrolled patients into study 306B.

Study Administration:
The Principle Investigator was Robert A Hauser, MD, University of South Florida, Parkinson's Disease and Movement Disorders Center (Tampa, Florida).

A Contract Research Organization (CRO), PPD development (North Carolina) was responsible for study planning, monitoring, clinical supply management, data management, medical monitoring, central laboratory services, interactive web response system, and electronic case report forms. Axio Research (Washington) was responsible for statistical analysis. PHT Corporation (Massachusetts) was responsible for designing, programming and managing patient electronic diaries and electronic clinician-reported outcome data. Fisher clinical Service Limited (Pennsylvania) was responsible for labeling and drug supply management. All study drugs were manufactured and packaged by Patheon (Ontario, Canada).

Primary Objective: Evaluate the clinical efficacy of droxidopa by improvement in the mean change in Orthostatic Hypotension Symptoms Assessment (OHSA) Item 1 from baseline to Visit 4 (Week 1) *(Note: this objective was revised from the original 306 and 306B protocols; see changes to Study 306).*

The OHSA scale was designed to rate symptoms occurring specifically as a result of low blood pressure over the previous week, using an 11-point scale (zero to 10), with more severe

symptoms scoring higher. Item 1 of the OHSA scale assesses the symptoms of dizziness, lightheadedness, feeling faint, or feeling like you might black out.

Eight Secondary Objectives:

1. Improvements in OHSA Item 1 across study visits
2. Difference in patient reported falls across study visits *(this secondary endpoint was revised from the original 306B protocol).*
3. Improvements in the Orthostatic Hypotension Questionnaire (OHQ) composite score, dizziness (OHSA Item 1) and activities of daily living (OHDAS Items 1 and 2) in patients who experience falls during the study and in the overall study population;
4. Change in symptom measurements using OHQ composite score, OHSA composite score and OHSA Items 2 to 6, and change in activity measurements using the Orthostatic Hypotension Daily Activity Scale (OHDAS) composite score and OHDAS items 1 to 4 across study visits;
5. Change in the clinical-reported and patient-reported Clinical Global Impressions-Severity (CGI-S) and the Clinical Global Impressions-Improvement (CGI-I) scales across study visits;
6. Evaluate effect on standing time—change across study visits
7. Evaluate effect on standing BP—change across study visits;
8. Safety and tolerability—occurrence of treatment-emergent adverse events (TEAE) and change in BP, HR, Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS_UPDRS), Parkinson's Disease Questionnaire-39 (PDQ-39), ECG, and laboratory measurements across the study.

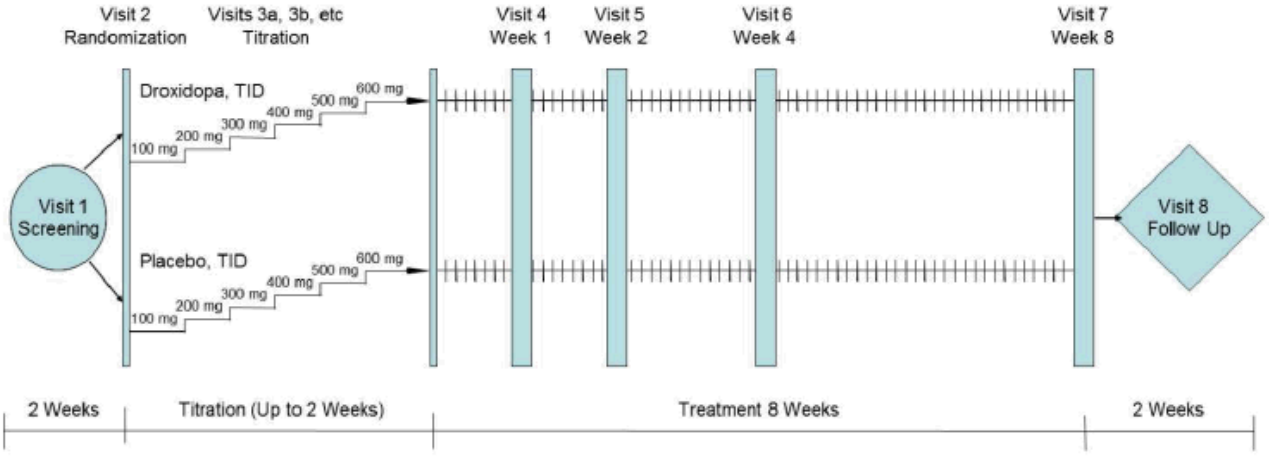


Figure 4. Study 306 design

At the end of the baseline visit, eligible patients were randomized (1:1) to either 100 mg TID droxidopa or placebo. Treatment was escalated in 100 mg TID increments until any one of the following:
1. The patient became completely asymptomatic for NOH symptoms on the clinician-reported CGI-S (defined as a score of 1-Normal, no OH)
2. The patient had SBP $\geq$ 180 mm Hg or DBP $\geq$ 110 mm Hg after 10 minutes in the supine position (head and torso elevated at about 30 degrees from horizontal) which was replicated 2 more times over an hour (or, at the Investigator's discretion, when BP was close to the limit).
3. The patient was unable to tolerate side effects believed related to study drug.
4. The patient reached a maximum dose of 600 mg TID.

Note: Titrations were based on a clinician's assessment of the patient's condition, rather than patient- assessed symptoms, using a global impression scale.

At each titration visit, patients underwent an Orthostatic Standing Test (OST) with standing time to be conducted 3 hours after their morning dose of study drug. The clinician CGI-S was to be completed before the OST.

Table 16. Study 306 schedule:

Table 9-3 Schedule of Assessments and Procedures

Study procedures	Screening Visit	Baseline Randomization Visit	Dose Titration Visits	Study Treatment Visits	End of Study Visit*	Post-study Follow-Up Visit
	(Visit 1)	(Visit 2)	(Visits 3a, 3b, 3c, etc.)	(Visit 4,5,6 and unscheduled)	(Visit 7)	(Visit 8)
Written informed consent	✓					
Review Inclusion and Exclusion Criteria	✓	✓				
Demography	✓					
Medical history	✓					
Concomitant medication	✓	✓	✓	✓	✓	
Adverse events (continuous monitoring)		✓	✓	✓	✓	✓
Physical examination	✓				✓	
Mini-mental state examination (MMSE)	✓					
Vital signs (BP, HR, temperature) and weight	✓	✓	✓	✓	✓	
Pregnancy Test for WOCP†	✓	✓††			✓	
12-lead ECG recording	✓			✓‡	✓	
Dose Titration Evaluation based on Clinician CGI-S			✓			
Orthostatic standing test with standing time (max 10 minutes)§		✓§	✓§	✓§	✓§	
Clinical symptoms – OHQ		✓		✓	✓	
Clinician- and patient-reported CGI-S		✓		✓	✓	
Clinician- and patient-reported CGI-I				✓	✓	
MDS-UPDRS and PDQ-39		✓			✓	
Blood and urine samples (laboratory safety)	✓			✓‡	✓	
Randomization		✓				
Dispense/review patient electronic diary		✓	✓	✓	✓	
Study drug dispensed, as required		✓	✓	✓		
Capsule count/compliance check			✓	✓	✓	
Study drug returned					✓	

BP=Blood pressure; CGI-I=Clinical Global Impressions-Improvement; CGI-S=Clinical Global Impressions-Severity; ECG=Electrocardiogram; HR=Heart Rate; Max=Maximum; MDS-UPDRS=Movement Disorder Society Unified Parkinson's Disease Rating; MMSE=Mini-Mental State Examination; OHQ=Orthostatic Hypotension Questionnaire; PDQ-39=Parkinson's Disease Questionaire-39; WOCP=Women of Childbearing Potential
* Or upon premature withdrawal from titration or treatment
§ If the Investigator considered that a patient could not, or was unlikely to be able to stand for 3 minutes, BP measurements should have been taken every 30 seconds (or as frequently as practical). In the event that the patient was unable to stand for 3 minutes, the last BP measurement should have been recorded in the CRF.
‡ Screening Visit, Visit 6, and Visit 7 or early termination only.
† Local urine pregnancy test (on site dip-stick test). Central lab serum pregnancy test only if urine test was positive.
†† Pregnancy tests were conducted predose.

Changes to study 306:
The original 306 study used the primary endpoint of change in OHQ composite score from baseline to Week 8. In accordance with the study plan, the Data Monitoring Committee (DMC) conducted an interim analysis after 60% of intended patients (n=51) had completed Visit 7 or were lost to follow-up. The purpose of this interim analysis was to evaluate safety data and assess assumptions regarding adequacy of the sample size for efficacy assessments.
Based on prespecified criteria, the analysis showed a conditional power of less than 0.1, which met the stopping criteria for futility. The DMC identified no safety issues of concern.

The PPD unblinded statistics team that was part of the Data Monitoring Committee had access to *all* Study 306 randomization codes during the time of the interim analysis. This included randomization codes for patients enrolled at the time of the interim analysis but not included in the interim analysis; those patients are included in study 306B. In the 306B study report, the sponsor states that "project-specific procedures were in place at the time to protect the blinding of the study within PPD. In addition, members of the biostatistics DMC support team were not members of the blinded project team."

A page of DMC minutes is shown below.

Droxidopa NOH306

DATA MONITORING COMMITTEE
CHAIR RECOMMENDATION FORM

Date of Meeting: 01 February 2011 DMC Chair: Aaron Miller, MD

Based upon the DMC review of the data provided for this Data Review Meeting, the following decisions and recommendations were agreed upon:	
Should the study continue?	Yes X☐ No ☐
Is additional follow up requested? *(Please specify under recommendations)*	Yes X☐ No ☐

Recommendations: The DMC met on Feb. 1, 2011 to consider a request by Chelsea for a recommendation to continue the trial with an amended protocol using the number of falls as a primary endpoint. The original trial design was based on a primary endpoint of change in the Orthostatic Hypotension Questionnaire. The DMC was mandated to conduct an interim analysis in accordance with the study plan when 50% of the intended patients had completed Visit 7. Based on the pre-stated criteria, the analysis showed a conditional power of less than 0.1, which was the stopping rule for futility. Therefore, the original recommendation of the DMC was that the study be discontinued on the basis of futility. The DMC identified no safety issues of concern.

Upon review of additional data, very encouraging results regarding secondary endpoints, especially a reduction in the number of falls, were observed in favor of the droxidopa group. The sponsor has proposed amending the protocol to change the primary endpoint to reduction in number of falls. The sponsor has proposed to include the patients currently remaining on treatment in the trial (a still blinded cohort) and to recruit additional patients to the trial, based on a power analysis. In view of the current absence of safety concerns and the promising results concerning falls in the analyzed cohort, the DMC concurs with the Sponsor's proposal and recommends continuing the trial, unless otherwise mandated by the FDA after its review of the submitted amendment, with the caveat of DMC review of the final and definitive calculations of the proposed number of additional patients to be recruited and continuation of the DMC charter for monitoring the efficacy and safety of the expanded trial.

Figure 5. Study 306 Data Monitoring Committee Chair Recommendation Form (February 1, 2011).

The sponsor states that "they were unblinded to all efficacy data for the 51 patients in the interim analysis….however, they remained blinded at all times to all data for patients in 306B until its completion."

In the submission, the sponsor conducted additional sensitivity analyses, where patient were excluded if they were enrolled at the time of the interim analyses (termed the Post-Interim Analysis Dataset, N=121).

The sponsor then split the study into two parts (306A and 306B), maintaining the same study design and patient population, but with a different primary endpoint and statistical analysis plan (SAP) in 306B.3

Protocol 306B (May 12, 2011) was planned with the primary objective of evaluating the difference between droxidopa and placebo in the rate of patient-reported falls from baseline to the end of study.

In a protocol amendment (November 5, 2012), the primary objective was changed to improvement in OHSA item 1, from baseline to Visit 4 (Week 1) and the difference in patient-reported falls across study visits became a secondary objective. The planned total sample size for 306B was 200 patients.

"Enrollment in the study was stopped prematurely and the data will be analyzed in accordance with an amendment to the statistical analytic plan. The protocol and statistical analytical plan have been amended, based on FDA feedback, to define the primary endpoint as change in dizziness/lightheadedness (OHSA item #1) from baseline to Week 1 (Visit 4) following 1 week of stable dose treatment. The sample size was re-estimated based on data from study 301 (PD patients only) to be 100 patients per arm (n=200 total) to demonstrate a difference of 1.1 units in the change in OHSA Item #1 from baseline to Week 1 (Visit 4) given a standard deviation of 2.8." (Source: protocol amendment).

Inclusion criteria: Male or female patients, at least 18 years old, with symptomatic NOH associated with PD. At their baseline visit (visit 2), subjects must have demonstrated a score of $\geq$ 3 on the composite OHQ, a score of $\geq$ 3 on the clinician CGI-S, and a fall of at least 20 mm Hg SBP or 10 mm Hg DBP within 3 minutes of standing.

Note: no entry criterion was specifically related to OHSA item 1.

Relevant exclusion criteria:

1. Score of 23 or less on the mini-mental state examination (MMSE);
2. Concomitant use of vasoconstricting agents such as ephedrine, dihydroergotamine, or midodrine; for the purpose of increasing BP;
3. Concomitant use of antihypertensive medication for the treatment of essential hypertension;
4. Change in dose, frequency or type of prescribed medication within 2 weeks of the baseline visit (Visit 2) except for vasoconstriction agents (e.g., ephedrine, dihydroergotamine or midodrine) or short courses (< 2 weeks) of treatments that do not interfere or exacerbate the subject's condition under study;

3 Chelsea Pharmaceutical staff involved in study 306 signed statements attesting that they did not

5. Sustained severe hypertension (SBP ≥ 180 mmHg or DBP ≥ 110 mm Hg in the supine or seated position observed in 3 consecutive measurements over an hour)
6. Congestive heart failure NYHA class III or IV
7. Unstable angina
8. Diabetic autonomic neuropathy
9. Myocardial infarction within the past 2 years
10. Significant uncontrolled arrhythmia

Study Treatments: Droxidopa and matching placebo were administered in doses of 100-600 mg TID. During the double-blind period, treatments were started at the 100 mg TID dose and escalated in 100 mg TID increments until a titration stopping rule was met; patients then continued their titrated dose of study drug through the 8-week double-blind period. Throughout the study, visit specific assessments were planned at 3 hours (range 2-5 hours) following the patient's first daily dose of study medication. In addition, patients received their assessments while in an "On" state relative to their anti-parkinsonian therapy (if the patient entered into an "Off" state, outstanding assessments were conducted when the patient returned to an "On" state).

Patients were randomized according to a computer-generated randomization schedule administered through a central IVRS.

Study Results:

Patient Disposition:

A total of 174 patients were randomized. A higher premature discontinuation rate was observed in droxidopa-treated subjects (see table below); the most common reason for withdrawal in both groups was adverse events. While ten droxidopa-treated subjects discontinued due to adverse events, two additional droxidopa patients who discontinued due to "withdrawing consent" were experiencing adverse events on the same day that they withdrew (see Table 30).

The "Other" category included noncompliance with medication as a reason for discontinuation.

There were more discontinuations prior to Visit 4 (Week 1) in the droxidopa group (n=18) compared to the placebo group (n=6) within the same time frame.

Table 17. Study 306B patient disposition

Table 10-1 Patient Disposition (All Patients)

	Placebo (N=85) n (%)	Droxidopa (N=89) n (%)	Total (n=174) n (%)
Total Patients Randomized	85 (100)	89 (100)	174 (100)
Total Patients Treated[1]	84 (98.8)	87 (97.8)	171 (98.3)
Completed Study[2]	67 (78.8)	62 (69.7)	129 (74.1)
Discontinued Study[3]	17 (20.0)	25 (28.1)	42 (24.1)
Reason for Discontinuation			
Treatment Failure	1 (1.2)	1 (1.1)	2 (1.1)
Adverse Event	6 (7.1)	10 (11.2)	16 (9.2)
Lack of Efficacy	2 (2.4)	4 (4.5)	6 (3.4)
Protocol Violation	0	1 (1.1)	1 (0.6)
Lost to Follow Up	1 (1.2)	0	1 (0.6)
Patient Withdrew Consent	1 (1.2)	3 (3.4)	4 (2.3)
Investigator Decision	1 (1.2)	2 (2.2)	3 (1.7)
Other	5 (5.9)	4 (4.5)	9 (5.2)

1. Three patients (1 placebo patient [Patient 111002] and 2 droxidopa patient [Patients 136001 and 159004]) were randomized but never treated.
2. Completed study is defined as completing 8 weeks of stable dose treatment.
3. Only patients treated are counted as discontinuing from the study.

Source: Table 1.1.

There was only one discontinuation due to "treatment failure" from the placebo group. Why so few placebo-treated patients discontinued because of treatment failure is not clear. Possible explanations include the presence of a placebo effect, variability in symptoms and/or misclassification of the reason for discontinuation.

The study population was about 2/3 male, mostly Caucasian (96%), elderly (mean age about 72 years, total range 41 to 92 years). Baseline OHSA item 1 was 5.1 units; lowest mean SBP within the first three minutes of standing was about 95-96 mm Hg. There were no baseline differences between the two groups in these parameters.

There were baseline imbalances between droxidopa and placebo in the Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part I (higher in placebo) and Parkinson's disease Questionnaire (PDQ-39) Scale (higher in placebo). The meaning of these imbalances is not clear and these scales are not part of the efficacy endpoints.

Concomitant medications: The most commonly used concomitant medication was Sinemet (carbidopa/levodopa), in 79% of both droxidopa and placebo patients. A total of 25 placebo (31%) and 30 droxidopa (34%) patients were taking rasagiline; and 6 patients in each group (7%) were on entacapone. Six placebo (7%) and 5 droxidopa (6%) patients were taking selegiline.

There was an imbalance of patients taking fludrocortisones at or post-baseline: 16 placebo (20%) and 30 (34%) droxidopa patients. Since fludrocortisone has been used to treat orthostatic hypotension, it is not clear whether this imbalance represents a between-group difference not captured elsewhere or a confounder.

According to the protocol (see exclusion criteria), patients were not to have changed dose/frequency/type of prescribed medication within two weeks of Visit 2.

Fludrocortisone acetate is a synthetic adrenocortical steroid possessing potent mineralocorticoid and high glucocorticoid activity. Adverse reactions include hypertension.

The most common reason for stopping dose titration was that the patient reached the maximum dose allowed without becoming asymptomatic—28 (41%) droxidopa-treated patients, 42 patients (54%) placebo-treated patients.

Titration was stopped in 29 (42%) droxidopa patients and 26 (33%) placebo patients due to the patients becoming asymptomatic—a difference of three patients between groups.

Four (6%) and 12 (15%) of droxidopa and placebo patients stopped further dose titration due to sustained hypertension.

Eight (12%) and 2 (3%) of droxidopa and placebo patients stopped titration due to inability to tolerate side effects.

87 (98%) of droxidopa and 78 (95%) placebo patients had at least one protocol deviation, most commonly deviations in study tests and procedures (~50%).

Less than half of those randomized to droxidopa were included in the per protocol population.

Table 18. Study 306B analysis populations:

Table 11-1 Analysis Populations

	Placebo (N=85)	Droxidopa (N=89)	Total (n=174)
Analysis Populations			
Safety Set[1]	82 (96.5)	89 (100.0)	171 (98.3)
Full Analysis Set[2]	78 (91.8)	69 (77.5)	147 (84.5)
Per Protocol Set[3]	45 (52.9)	34 (38.2)	79 (45.4)

Note: Percentages for the analysis populations are based on the number of patients randomized in each group.

1. The Safety Set consists of all patients who received at least one dose of study drug. Two patients (110006 and 153007) were randomized to placebo but received some droxidopa; these are included in the droxidopa treatment arm for the Safety Set. Three patients (1 placebo patient [Patient 111002] and 2 droxidopa patients [Patients 136001 and 159004]) were randomized but never treated.
2. The Full Analysis Set (FAS) is a modified intent-to-treat set, consisting of all randomized patients who received at least one dose of study drug and reported OHSA Item 1 data at Week 1.
3. The Per Protocol (PP) Set consists of patients in the FAS who did not have major protocol violations and were compliant with study treatment. Compliance was defined as a patient taking at least 80% of their planned study drug doses during the first 4 weeks and at least 80% of their planned study drug doses during the final 4 weeks.

Source: Table 1.1.

A total of 20 droxidopa and 7 placebo patients were excluded from the full analysis set.

Mean compliance was about 97% for both groups (assessed by capsule count).

The primary efficacy endpoint: mean change from baseline to Week 1 in OHSA item 1 score (11 point scale, 0-10). Missing data were excluded from this analysis.

Week 1 was measured after the 1-2 week open-label titration; hence, Week 1 really connotes 2-3 weeks of droxidopa treatment (or exposure).

Droxidopa-treated patients showed mean decrease from baseline of 2.3 units, indicating improvement, compared with 1.3 unit decrease in placebo patients—an unadjusted treatment difference of 1.0 units favoring droxidopa.

Table 19. Study 306B: Primary efficacy analysis

	Droxidopa			Placebo		
	N	Mean	STD	N	Mean	STD
Baseline	69	5.1	2.04	78	5.1	2.33
Week 1	69	2.8	2.44	78	3.8	2.75
Least square mean difference	-0.94 with 95% CI (-1.78, -0.1)					
p-value from ANCOVA model	0.028					

(Source: primary statistical review: Dr. Jialu Zhang).

The primary analysis excluded missing data, since OHSA item 1 was not measured during the titration phase.

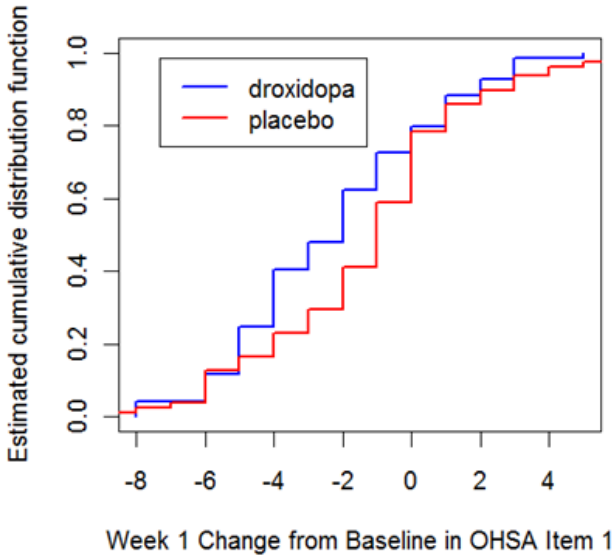


Figure 6. Cumulative distribution of the primary endpoint (Change from baseline to Week 1 in OHSA item-1) (source: primary statistical review: Dr. Jialu Zhang).

From the cumulative distribution of the change in OHSA item 1 from Baseline to Week 1, the two curves (droxidopa above, placebo below) show separation between -4 (improvement) and zero (no change).

According to the statistical reviewer, the intra-subject variability was calculated at 2.9, higher than the Week 1 treatment effect.

For both droxidopa and placebo, there appears to be a linear relationship between baseline OHSA item 1 and improvement with therapy.

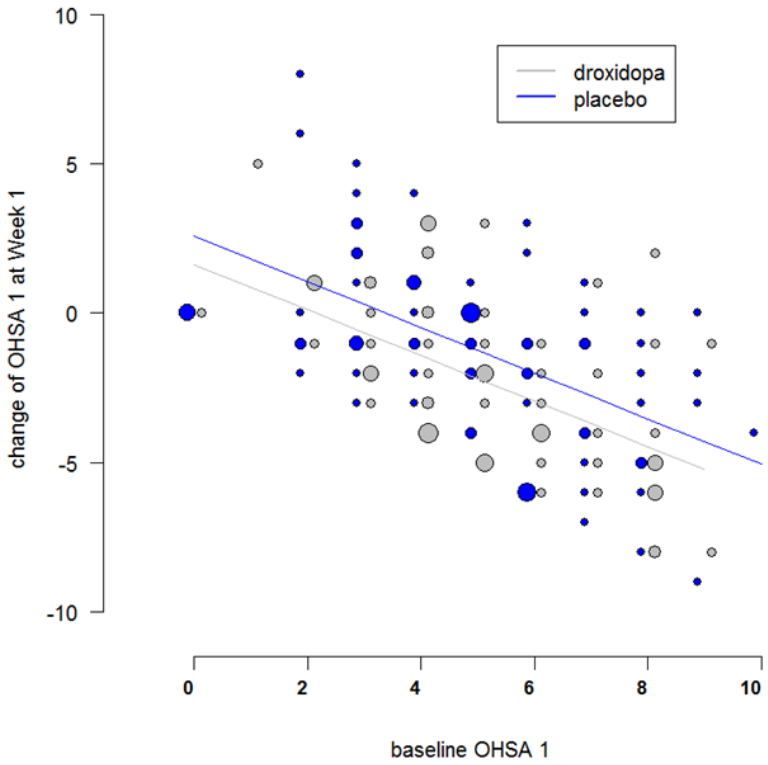


Figure 7. The change from baseline to Week 1 in OHSA item-1 as a function of baseline OHSA item-1 (source: primary statistical review: Dr. Jialu Zhang)

According to the sponsor's analysis, significantly more droxidopa patients (vs. placebo) had an improvement of at least 4 units in OHSA item 1 from baseline to Week 1:

Table 20. Study 306B: Responder analysis:

	OHSA Item 1 Unit Improvements		
	Placebo (N=78) N (%)	Droxidopa (N=69) N (%)	P-value
≥1 Unit Improvement from Baseline			0.118
Yes	46 (59.0)	50 (72.5)	
No	32 (41.0)	19 (27.5)	
≥2 Unit Improvement from Baseline			0.013
Yes	32 (41.0)	43 (62.3)	
No	46 (59.0)	26 (37.7)	
≥3 Unit Improvement from Baseline			0.027
Yes	23 (29.5)	33 (47.8)	
No	55 (70.5)	36 (52.2)	
≥4 Unit Improvement from Baseline			0.032
Yes	18 (23.1)	28 (40.6)	
No	60 (76.9)	41 (59.4)	

To address the imbalance in missing data, the statistical reviewer used imputation by carrying forward the baseline observations. The resulting treatment effect using this analysis was calculated as -0.45 with 95% confidence intervals (-1.2, 0.3).

Table 21. Study 306B: Primary Endpoint: OHSA item 1 (FAS) by fludrocortisone use (yes/no):

Change from baseline to Week 1 (primary analysis)	Placebo (N=78)	Droxidopa (N=69)	Difference from placebo (95% CI)	Non-parametric p-value
No fludrocortisone	N=65	N=51		
Adjusted mean	-1.4	-2.2	-0.7 (-1.7, 0.2)	0.065
Fludrocortisone	N=13	N=18		
Adjusted mean	-0.5	-2.5	-1.9 (-4.0, 0.2)	0.064

(Source: sponsor)

The smaller effect size in the "no fludrocortisone" subgroup appears to be driven by the larger placebo effect in this subgroup. Fludrocortisone use does not appear to have contributed to the OHSA item-1 result for patients on placebo; the effect (if any) in patients treated with droxidopa appears to be small. However, one cannot exclude other baseline differences between the groups (e.g., severity of disease, etc) that led to the imbalance in fludrocortisone use.

Secondary Endpoints:

Improvements in OHSA Item 1 across study visits: as shown below, the treatment effect in Week 1 (study 306B) appears to go away by Week 2; one can observe the respective placebo and droxidopa means and 95% confidence intervals merge together.

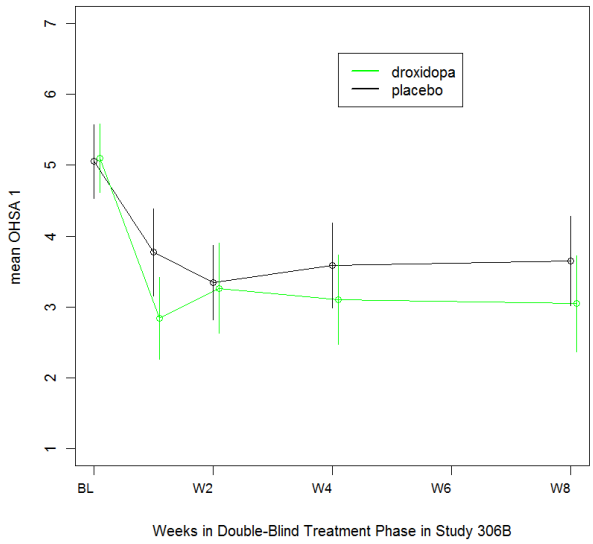


Figure 8. Study 306B: Mean OHSA item-1 by treatment and study visit

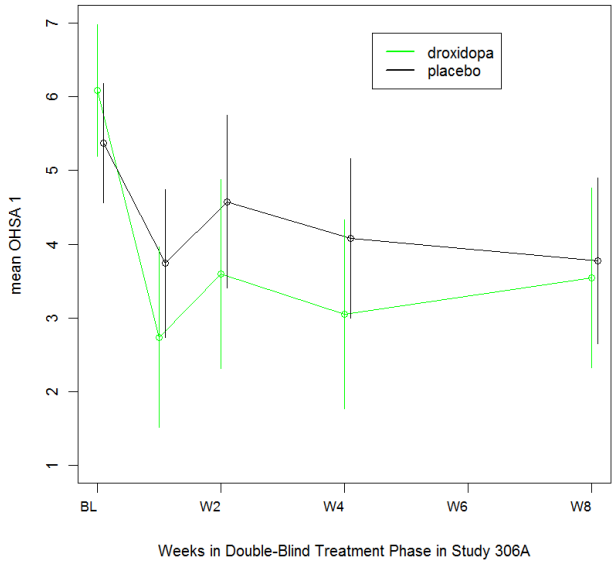


Figure 9. Study 306A: Mean OHSA item-1 by treatment and study visit

The curves for OHSA item-1, OHQ and SBP are not consistent between studies 306A and 306B.

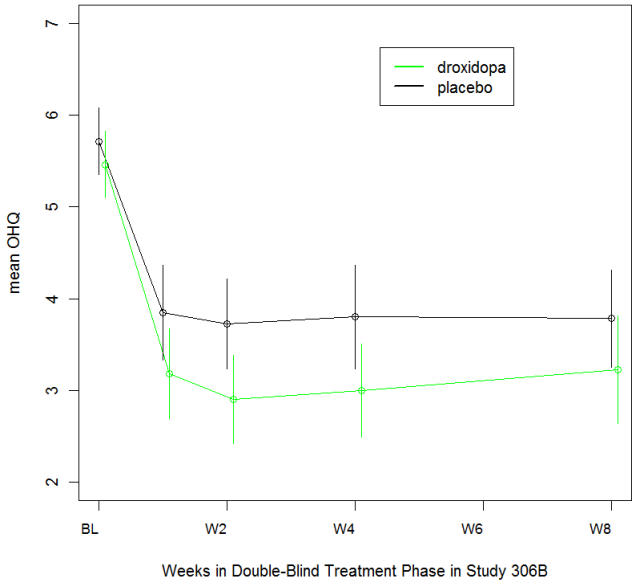


Figure 10. Study 306B: Mean OHQ by treatment and study visit

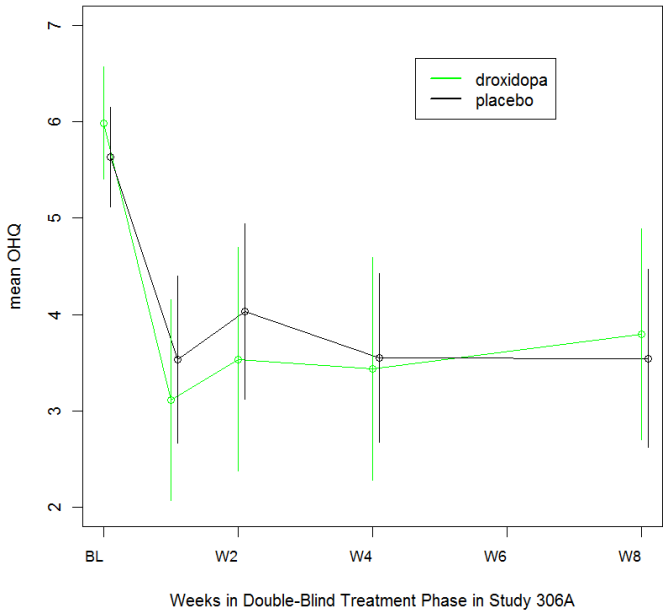


Figure 11. Study 306A: Mean OHQ by treatment and study visit

Mean (95% confidence intervals) of the lowest standing SBP between 0 and +3 minutes of

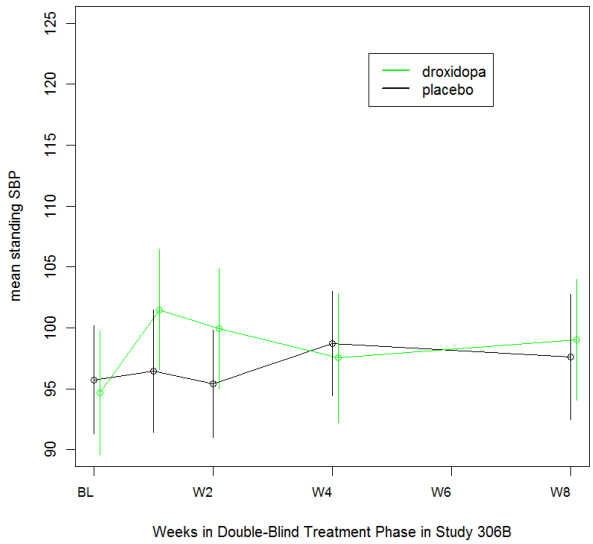


Figure 12. Study 306B: Mean (95% confidence intervals) of the lowest standing SBP between 0 and +3 minutes of standing by visit and treatment group.

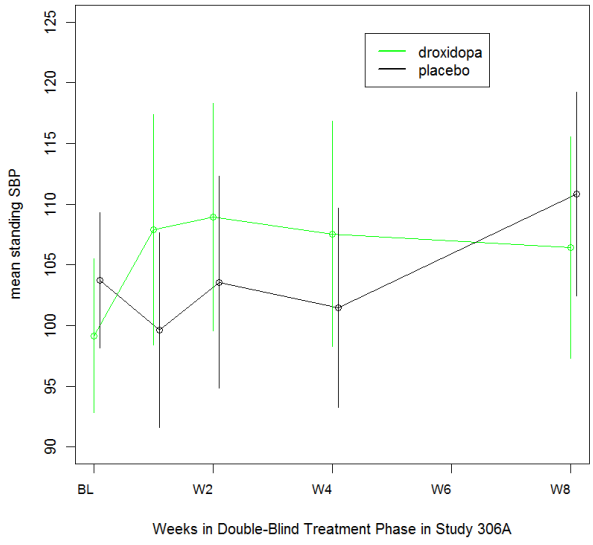


Figure 13. Study 306A: Mean (95% confidence intervals) of the lowest standing SBP between 0 and +3 minutes of standing by visit and treatment group.

Table 22. Study 306B: Comparison of efficacy results at different time points:

	Whole Study Population		Sponsor's Post Interim Analysis		Reviewer's Post Interim Analysis		Revoking Access to Treatment Code		Changing Primary Endpoint	
			After Nov 10, 2010		After Dec 14, 2010		After March 2, 2011		After May 12, 2011	
	N=147		N=121		N=113		N=93		N=71	
	trt eff est	CI	trt eff est	CI	trt eff est	CI	trt eff est	CI	trt eff est	CI
OHSA Item 1: Mean change from baseline at Week 1	-0.9	(-1.8, 0.1)	-1.1	(-2.0, -0.1)	-1.0	(-2.0, -0.05)	-0.6	(-1.7, 0.5)	-0.7	(-2.0, 0.6)
Lowest standing SBP between 0 to 3 minutes at Week 1	5.4	(-0.5, 11.3)	5.8	(-0.9, 12.4)	5.0	(-2.0, 12.0)	2.5	(-5.0, 10.0)	0.8	(-8.5, 10.1)
OHQ mean change from baseline at Week 1	-0.6	(-1.2, 0.1)	-0.7	(-1.5, 0.03)	-0.7	(-1.4, 0.1)	-0.4	(-1.2, 0.4)	0.3	(-1.3, 0.7)
Clinician-reported CGI-S at Week 1	-0.4	(-0.8, -0.05)	-0.5	(-0.9, -0.1)	-0.5	(-0.9, -0.1)	-0.4	(-0.9, 0.03)	-0.2	(-0.7, 0.3)
Patient-reported CGI-S at Week 1	-0.4	(-0.8, 0.02)	-0.5	(-0.9, -0.04)	-0.5	(-0.9, -0.02)	-0.4	(-1.0, 0.1)	-0.2	(-0.8, 0.4)
Clinician-reported CGI-I at Week 1	-0.5	(-0.9, -0.1)	-0.6	(-1.0, -0.2)	-0.7	(-1.1, -0.2)	-0.5	(-1.0, -0.1)	-0.4	(-1.0, 0.1)
Patient-reported CGI-I at Week 1	-0.2	(-0.5, 0.1)	-0.3	(-0.7, 0.01)	-0.3	(-0.7, 0.02)	-0.2	(-0.6, 0.2)	-0.2	(-0.7, 0.3)

The review team considered the effects of the unblinded interim analysis and access to the randomization codes on the efficacy endpoints.

The mean OHSA item 1 and SBP treatment effects appear smaller after revocation access to treatment codes. The patient-reported CGI-I appears to be consistently lower than the clinician-reported CGI-I throughout the various time points.

Patient-reported falls:

Patient-reported falls were captured using an electronic diary on a daily basis from baseline to the end of the 8-week treatment period. The dataset included capture of freezing; however, this reviewer was unable to discern a relationship between freezing and falls (not shown).

Table 23. Study 306B: Summary of Patient-reported falls (FAS)

Table 11-11 Summary of Patient-Reported Falls Data (FAS[1])

Analysis	Placebo (N=78)[2]	Droxidopa (N=69)[1]
Total Number of Falls, n	716	229
Percentage of Patients with ≥1 Fall[3], n (%)	47 (60.3)	40 (58.0)
Mean Patient Rate of Falls Per Patient-Week[4]	2.0 (12.95)	0.4 (0.84)
Cumulative Count of Falls[5], n		
By End of Titration	232	46
By Week 4	586	140
By Week 8	716	229

FAS=full analysis set; Max=maximum; MDE=missing data excluded; Min=minimum; SD=standard deviation.
1. Missing data were excluded.
2. All subjects had evaluable records defined as any non-missing response in the daily falls diary.
3. Percentages are based on the number of patients with any evaluable record.
4. Aggregate rate of falls is calculated over all patients in each treatment arm as the (total number of falls/number of evaluable days)*7. Patient rate of falls is calculated for each patient as the (total number of falls/number of evaluable days)*7.
5. Number of falls by each week is cumulative, i.e., a patient who fell during Week 1 also fell by Week 2.

Source: Table 2.2.2.

The frequency distributions of falls appear similar between groups; however, there were two placebo "outlier" patients with 118 and 358 falls, respectively, during the 8 week study. These two placebo outliers likely affected results for the total number of falls, mean patient rate, and cumulative fall counts. There were no statistically significant differences between droxidopa and placebo in the total number of falls; in the rate ratio (placebo/droxidopa) in aggregate number of falls per patient-week; or in the falls per patient-week.

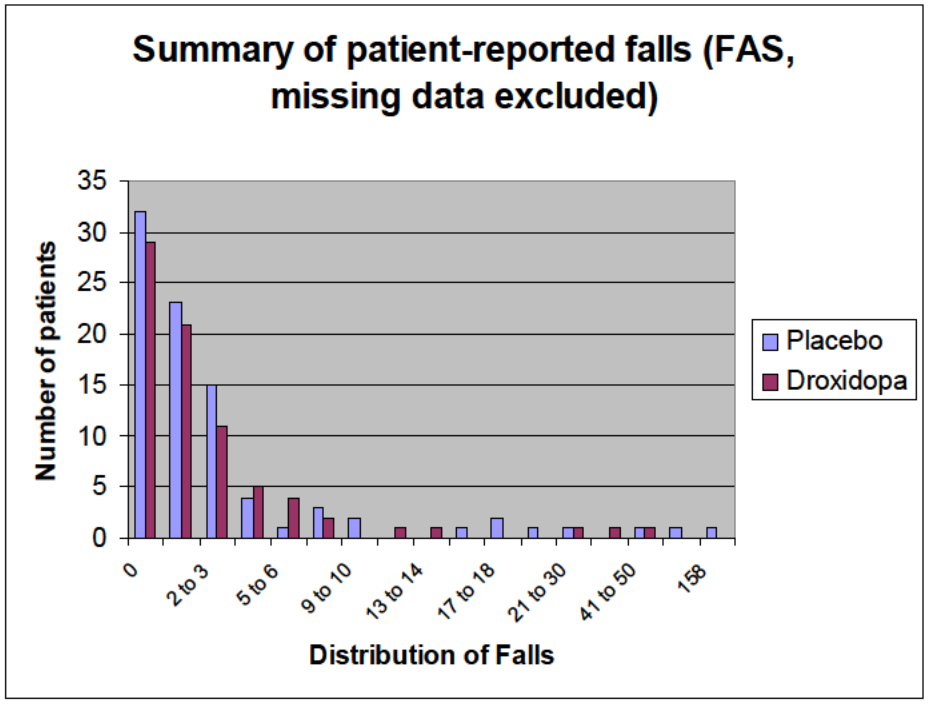


Figure 14. Study 306B: Frequency distribution of patient-reported falls from baseline to Week 8 (FAS, missing data excluded). Source: sponsor: table 2.2.2.

The median fall rates are the same between placebo and droxidopa-treated patients in the sensitivity analyses performed when the top 2, 5 and 10 patients were removed:

Table 24. Study 306B: Sponsor's sensitivity analyses for patient-reported falls (FAS)

Table 11-12 Sensitivity Analyses for Patient-Reported Falls (306B, FAS[1])

Analysis	Placebo (N=78)	Droxidopa (N=69)	Rate Ratio (Placebo/ Droxidopa)	p-value
Top 2 Subjects with Most Falls Removed[2]	N=76	N=67	---	---
Rate of Falls per Patient-Week[3], n	0.37	0.25	1.47	0.827[4]
Rate of Falls Per Patient-Week				
Mean (SD)	0.4 (0.78)	0.3 (0.47)	---	---
Median (Min, Max)	0.1 (0.0, 3.8)	0.1 (0.0, 3.1)	---	---
Top 5 Subjects with Most Falls Removed[2]	N=73	N=64	---	---
Rate of Falls per Patient-Week[3], n	0.25	0.17	1.53	0.808[4]
Rate of Falls Per Patient-Week				
Mean (SD)	0.3 (0.55)	0.2 (0.24)	---	---
Median (Min, Max)	0.1 (0.0, 3.3)	0.1 (0.0, 1.0)	---	---
Top 10 Subjects with Most Falls Removed[2]	N=68	N=59	---	---
Rate of Falls per Patient-Week[3], n	0.15	0.12	1.29	0.778[4]
Rate of Falls Per Patient-Week				
Mean (SD)	0.2 (0.42)	0.1 (0.17)	---	---
Median (Min, Max)	0.1 (0.0, 3.3)	0.1 (0.0, 0.8)	---	---

FAS=full analysis set; Max=maximum, Min=minimum, SD=standard deviation.
1. Missing data were excluded.
2. All subjects had evaluable records defined as any non-missing response in the daily falls diary.
3. Rate of falls per patient-week is calculated as the (total number of falls/number of evaluable days)*7.
4. Assumptions of negative binomial were not satisfied; p-value is from non-parametric Wilcoxon rank sum test.

Source: Table 4.3.1, Table 4.3.2, and Table 4.3.3.

The sponsor has reported a higher proportion of placebo patients experiencing a fall-related injury (26%) compared with patients treated with droxidopa (17%), including 2 placebo patients with fractures and 1 with traumatic brain injury compared to zero events on droxidopa. However, one cannot exclude the possibility of fall events that were not captured in those that prematurely discontinued treatment.

Standing Time during the OST: The mean baseline standing time for placebo and droxidopa groups were 8.9 and 9.2 minutes, respectively; the median standing time was 10.0 minutes at baseline and at Weeks 1, 2, 4 and 8. The mean change from baseline to Week 1 in standing time was zero for both groups; there was no statistically significant difference between the two groups at the measured time points.

Safety:

A total of 171 patients (84 placebo, 87 droxidopa) were treated in 306B. Two placebo patients mistakenly received droxidopa due to site errors—Patient 110006 received droxidopa for 3 days and patient 153007 received droxidopa for an estimated 12 days.

During titration, the mean overall duration of exposure was 10.7 days for droxidopa and 10.4 days for placebo.

Exposure: The mean duration of droxidopa treatment was 52.4 days versus a longer duration, 59.5 days, on placebo. Median durations were comparable.

Table 25. Study 306B: Summary of Exposure (safety set)

Table 12-1 Summary of Exposure - All Patients (Safety Set)

	Placebo (N=82)	Droxidopa (N=89)
Last Titration Dose, n (%)		
100 mg	7 (8.5)	9 (10.1)
200 mg	8 (9.8)	7 (7.9)
300 mg	11 (13.4)	15 (16.9)
400 mg	7 (8.5)	18 (20.2)
500 mg	10 (12.2)	5 (5.6)
600 mg	39 (47.6)	35 (39.3)

	Placebo (N=82)	Droxidopa (N=89)
Duration of Exposure in Titration Period (days)		
n	82	89
Mean (SD)	10.4 (4.44)	10.7 (4.17)
Median	10.5	10.0
Min, Max	2, 23	1, 20
Duration of Exposure at Stable Dose [1] (days)		
n	82	89
Mean (SD)	52.0 (17.65)	44.3 (23.21)
Median	58.0	57.0
Min, Max	2, 78	2, 71
Duration of Exposure Overall [2] (days)		
n	82	89
Mean (SD)	59.5 (18.82)	52.4 (24.52)
Median	66.0	65.0
Min, Max	2, 79	2, 78
Duration of Exposure Overall, [3] n (%)		
≥ 7 days	79 (96.3)	84 (94.4)
≥ 14 days	77 (93.9)	77 (86.5)
≥ 21 days	75 (91.5)	70 (78.7)
≥ 28 days	74 (90.2)	66 (74.2)
≥ 35 days	71 (86.6)	66 (74.2)
≥ 42 days	70 (85.4)	65 (73.0)
≥ 49 days	68 (82.9)	64 (71.9)
≥ 56 days	68 (82.9)	62 (69.7)

Max=Maximum; Min=Minimum; SD=Standard deviation; TID=Three times daily.
Patients who had a dose reduction are counted based on their dose at the start of the double-blind treatment period.
1. Duration of exposure to study drug at stable dose was defined as the duration of exposure to study drug at the dose at the end of titration, calculated as the number of days from the date of the first dose at this level to the last dose date for the double-blind treatment period.
2. Duration of exposure overall was calculated as the number of days of study drug exposure from the beginning of titration to the end of double-blind treatment period + 1 day.
3. Exposure was cumulative, i.e., patients with at least 2 weeks of exposure also had at least 1 week of exposure.
Source: Table 1.7.

Deaths:
No deaths occurred during study 306B or 306A.

Nonfatal Serious Adverse Events (SAE):

All patients in 306B reporting SAE were over 60 years old. Five patients in the droxidopa group reported a total of 9 SAEs, and four patients in the placebo group reported five SAEs. Patient 110006 was randomized to placebo but mistakenly received droxidopa for 3 days during titration, returned to placebo treatment for 3 days, then had an SAE (atrial fibrillation); this event was included in the droxidopa treatment group in all Safety Set tables.

Table 26. Study 306B: Serious adverse events:

Patient ID	Age	Gender	Treatment	Dose (TID)	PT	Study Day	Action
122013	80	F	Placebo	300 mg	Syncope	3	None
132027	86	M	Placebo	300 mg	Viral infection	57	None
146006*	62	M	Placebo	600 mg	Fibula fracture	33	Discontinued
					Syncope	33	
151007	82	M	Placebo	600 mg	Asthenia	70	Interrupted
110006¶	77	M	Droxidopa	300 mg	Atrial fibrillation	12	Discontinued
146008	70	M	Droxidopa	100 mg	Faecaloma	32	Interrupted
146010	59	M	Droxidopa	100 mg	Inguinal hernia	5	Interrupted
156007**	76	M	Droxidopa	400 mg	Upper respiratory tract infection	15	None
					viral bronchitis		
					Altered mental status	20	Discontinued
					Presyncope		
184003	79	F	Droxidopa	300 mg	Abdominal pain upper	5	None
					Hypertension		Discontinued

*The sponsor separated these two AE, which occurred on the same study day.
** coded for two AEs, URI and viral bronchitis, same AE day, likely related to one event. Patient 156007: Altered mental status and presyncope, coded separately, occurred on the same day (11/20/2010). According to Listing 16.4.32 (CSR page 959 of 982), study drug was discontinued because of mental status changes but no action was taken for presyncope. However, because both SAE occurred on the same day, the medical reviewer is linking the two events.
¶ Randomized to the placebo group, but mistakenly treated with droxidopa for 3 days.

Two SAEs might be related to effects of droxidopa (e.g., hypertension, atrial fibrillation).

Table 27. Study 306B: Treatment-emergent adverse events:

Preferred term	Placebo N= 82	Droxidopa N= 89
	n (%)	n (%)
Total	65 (80)	73 (82)
Headache	6 (7)	12 (14)
Dizziness	4 (5)	9 (10)
Nausea	2 (2)	7 (8)
Gait disturbance	0	4 (5)
Contusion	10 (12)	4 (5)
Skin laceration	7 (9)	3 (3)
Hypertension	1 (1)	7 (8)

Events included if ≥3% of patients in the droxidopa group and difference between groups ≥ 3 patients (safety set).

Note: A higher incidence of gait disturbance and dizziness in patients treated with droxidopa seems paradoxical to the purported benefits of droxidopa in decreasing orthostatic symptoms.

Table 28. Study 306B: Treatment-emergent adverse events during titration

Preferred term	Placebo N=82 n (%)	Droxidopa N=89 n (%)
Total number with TEAE	32 (41)	53 (60)
Headache	3(4)	9 (10)
Dizziness	1 (1)	6 (7)
Parkinson's disease	1 (1)	3 (3)
Nausea	2 (2)	6 (7)
Diarrhea	0	3 (3)
Fatigue	4 (5)	6 (7)
Hypertension	0	4 (5)
Insomnia	1 (1)	3 (3)

Events included if ≥ 3% of patients in the droxidopa group (safety set):

There were more adverse events on droxidopa. In addition, more patients on droxidopa experienced AE leading to discontinuations. Of the 10 discontinuations from droxidopa, 5 were due to hypertension or supine hypertension; two were related to hallucination or vivid dreams; and one was due to altered mental status. All subjects in this listing were aged 62 years and older.

Table 29. Study 306B: Adverse events leading to discontinuation:

Patient #	Treatment	Preferred term	Study day	Dose TID	Outcome
115004	Droxidopa	Worsening of hallucination	10	200 mg	Resolved
131005	Droxidopa	Hypertension	20	600 mg	Ongoing
132004	Droxidopa	Supine hypertension	5	100 mg	Resolved
141004	Droxidopa	Worsening of vivid dreams	19	100 mg	Resolved
152004	Droxidopa	Hypotension	15	400 mg	Ongoing
156002	Droxidopa	Elevated BP	1	100 mg	Ongoing
156007	Droxidopa	Altered mental status	20	400 mg	Resolved
160003	Droxidopa	Elevated BP	20	300 mg	Ongoing
182008	Droxidopa	Worsening of Parkinson's	5	500 mg	Ongoing
184003	Droxidopa	Hypertension	3	300 mg	Resolved
110006*	Droxidopa	Atrial fibrillation	12	300 mg	Resolved
146006	Placebo	Syncopal episode	33	600 mg	Resolved
160006	Placebo	Hypertension	19	400 mg	Ongoing
160005	Placebo	Increased BP	5	100 mg	Resolved
161005	Placebo	Malaise	2	100 mg	Ongoing
176003	Placebo	Gastroenteritis	8	400 mg	Resolved

Source: AE.xpt and SURRAND.xpt

*Randomized to placebo, but mistakenly treated with droxidopa for 3 days, therefore analyzed for safety in droxidopa group.

Note: Subject #156007, altered mental status, was not coded as an SAE. According to the narrative, "While sitting at the breakfast table, the patient was observed by wife to be unresponsive, like in a daze and pale in color. The patient was not aware of his surroundings. CT of head, blood work, CXR."

Case report forms for premature discontinuations for reasons other than adverse events were reviewed. In some cases, an adverse event was recorded on the same day that a patient withdrew consent.

Table 30. Study 306B: Premature Discontinuations coded other than due to AE:

Subject number	Treatment	Randomized	Termination	Reason in listing	Comment
100003	Placebo	3/28/2012	4/30/2012	Lost to follow up	Abdominal pain 5/17/2012 (not serious)
112001	Placebo	20/26/2010	12/9/2010	Lack of efficacy	Exacerbation of intermittent headaches (10/24/2010-1/1/2011).
112003	Placebo	4/17/2012	5/17/2012	Lack of efficacy	Fatigue, 4/28/2012-ongoing; bilateral lower leg aches, 4/25/2012-7/30/2012; psoriasis, 4/28/2012-ongoing; thinning hair, 5/4/2012-ongoing; small burn right cheek,

					5/4/2012-5/29/2012.
112004	Placebo	5/8/2012	5/10/2012	Other	Investigator decision due to borderline blood pressure.
122008	Placebo	11/24/2010	1/3/2011	Investigator decision	Inconsistent with compliance and reporting falls.
122014	Placebo	1/24/2011	1/27/2011	Other	Blood pressure over 180. No adverse events recorded.
132027	Placebo	1/23/2012	4/13/2012	Other	Bilateral ear congestion (1/24/2012-4/19/2012); terminated because study med not restarted while patient in rehab facility.
146007	Placebo	8/8/2011	9/16/2011	Patient withdrew consent	Double vision 8/17/2011-9/20/2011; visual hallucinations 8/10/2011-9/20/2011; pneumonia 9/12-29/2011. Cognitive impairment 8/24/2011-ongoing.
153007	Droxidopa	1/3/2011	2/22/2011	Other	Allocated wrong bottle; bladder tumor
161002	Placebo	5/4/2011	6/15/2011	Other	Entered extension study 6/15/2011. Terminated because patient wanted to leave town for 3 months.
183004	Placebo	1/25/2011	2/10/2011	Treatment failure	Lower respiratory infection 2/5/2011-2/16/2011; dehydration 2/8/2011-2/11/2011; ecchymosis left hip 2/6/2011-2/13/2011.
110004	Droxidopa	7/15/2011	7/23/2011	Patient withdrew consent	No adverse events recorded.
113008	Droxidopa	8/10/2011	8/12/2011	Other	Intermittent headaches recorded, "unlikely related."
118004	Droxidopa	12/17/2010	1/4/2011	Investigator decision	Patient did not demonstrate dosing compliance.
132010	Droxidopa	12/13/2010	12/23/2010	Lack of efficacy	No adverse events recorded.
140001	Droxidopa	11/1/2010	11/2/2010	Patient withdrew consent	Intermittent lightheadedness, (11/2/2010) increased study drug, resolved.
142003	Droxidopa	10/1/2010	10/25/2010	Other	10/25/2010: AE intermittent kidney stones, resolved 4/11/2011; urinary bladder stones, 10/25/2010-11/19/2010.
160001	Droxidopa	12/16/2010	12/22/2010	Protocol violation	No adverse events recorded.
164005	Droxidopa	11/17/2010	12/1/2010	Patient withdrew consent	Headache x 1 hour after taking first dose study medication/each day (11/18/10-12/1/10).

Source: clinical review of patient case report forms. Adverse events recorded around the time of study termination are shown in this table.

Laboratory Results:
A review of shift tables revealed 7 droxidopa-treated patients with normal baseline and elevated sodium values at the Week 8 (Visit 7) time point. There were no placebo patients with normal baseline and elevated post-treated sodium values; two placebo patients with normal baseline sodium values had lower post-treatment values. The highest sodium value, 150 mEq/L, was reported for a droxidopa-treated patient at the end of study visit (Visit 7); the other elevated sodium values were in the range of 146-148 mEq/L, where the upper limit of normal was 145 mEq/L. Otherwise, no trends in laboratory results were observed with droxidopa therapy. However, a large amount of missing Week 4 results were noted with respect to results such as glucose, sodium, liver enzymes, BUN, creatinine (20% of placebo; 29% of droxidopa); at the Week 8 time point about 6% of chemistry laboratory results were missing.

The sponsor has reported a shift to high total neutrophils at Week 4 (10 droxidopa patients and 5 placebo patient) and Week 8 (4 droxidopa patients and 1 placebo patient) for droxidopa-treated patients compared to those on placebo. It is not clear whether these shifts are clinically meaningful and related to droxidopa.

Heart rate: Based on available vital sign collection and electrocardiograms, there does not appear to be clinically meaningful changes in heart rate in patients treated with droxidopa vs. those on placebo. However, Week 4 ECGs were missing in 12% of placebo and 27% of droxidopa patients; and Week 8 ECGs were missing in 16% of placebo and 32% of droxidopa patients.

Comments:
1. Study 306B was a randomized, double-blind, placebo-controlled study of 1-2 weeks titration followed by 8 weeks of treatment at the titrated dose. The primary endpoint of the original study 306 was changed twice.
2. More droxidopa-treated patients discontinued prematurely compared to those on placebo. The most common reason for discontinuation was due to adverse events; half of those were due to hypertension.
3. Study 306B met its amended primary endpoint, OHSA item-1, with a treatment effect of -0.9 on an 11 point scale.
4. There was a higher number and percentage of droxidopa-treated patients taking concomitant fludrocortisone compared with those on placebo. The role of this imbalance is not clear, but the imbalance raises questions about comparability between groups and the possibility of confounding.
5. The intra-subject variability for the primary endpoint, OHSA item-1, is larger than the treatment effect.
6. The primary endpoint, systolic BP and the composite OHQ do not show consistent effects or durability beyond 2 to 3 weeks of treatment (beyond Week 1 of 306B).
7. The most common adverse events in study 306B were: hypertension, headache, nausea and dizziness.

9.2 Glossary of outcome instruments

9.2.1 Orthostatic Hypotension Questionnaire (OHQ):

The OHQ questionnaire includes specific instructions that are read aloud to the patients before the questions are answered, and is administered in two separate sections: a symptom assessment scale and a daily activity scale. The OHQ composite score is a mean of the OHSA composite and the OHDAS composite scores:

9.2.1.1 The Orthostatic Hypotension Symptom Assessment (OHSA)

The OHSA scale was designed to rate symptoms occurring as a result of low blood pressure, using an 11-point scale (zero to 10), with more severe symptoms scoring higher. The scale assesses six symptoms: 1. Lightheadedness/Dizziness; 2. Problems with vision; 3. Weakness; 4. Fatigue; 5. Trouble concentrating; and 6. Head/neck discomfort.

9.2.1.2 The Orthostatic Hypotension Daily Activity Scale (OHDAS)

The OHDAS was designed as a measure of quality of life. This instrument uses an 11-point scale to assess whether orthostatic hypotension (OH) "interfered" with four types of activities: 1. Standing for a short time; 2. Standing for a long time; 3. Walking for a short time; and 4. Walking for a long time. A zero rating means that over the preceding week the activity was performed with no interference; a "ten" rating means that OH completely interfered with the activity. Patients can also check a box stating that they could not perform the activity for reasons other than OH. Scores for each activity and a composite score for all 4 activities are tabulated.

I. **The Orthostatic Hypotension Symptom Assessment (OHSA)**

Please circle the number on the scale that best rates how severe your symptoms from low blood pressure have been ***on the average*** over the past week. Please respond to every symptom. If you do not experience the symptom, circle zero (0). PLEASE RATE THE SYMPTOMS THAT ARE DUE ONLY TO YOUR LOW BLOOD PRESSURE PROBLEM.

1. Dizziness, lightheadedness, feeling faint, or feeling like you might black out

None 0 1 2 3 4 5 6 7 8 9 10 Worst Possible

2. Problems with vision (blurring, seeing spots, tunnel vision, etc.)

None 0 1 2 3 4 5 6 7 8 9 10 Worst Possible

3. Weakness

None 0 1 2 3 4 5 6 7 8 9 10 Worst Possible

4. Fatigue

None 0 1 2 3 4 5 6 7 8 9 10 Worst Possible

5. Trouble concentrating

None 0 1 2 3 4 5 6 7 8 9 10 Worst Possible

6. Head/neck discomfort

None 0 1 2 3 4 5 6 7 8 9 10 Worst Possible

II. The Orthostatic Hypotension Daily Activity Scale (OHDAS)

We are interested in how the low blood pressure symptoms you experience affect your daily life. Please rate each item by circling the number that best represents how much the activity has been interfered with *on the average* over the past week by the low blood pressure symptoms you experienced.

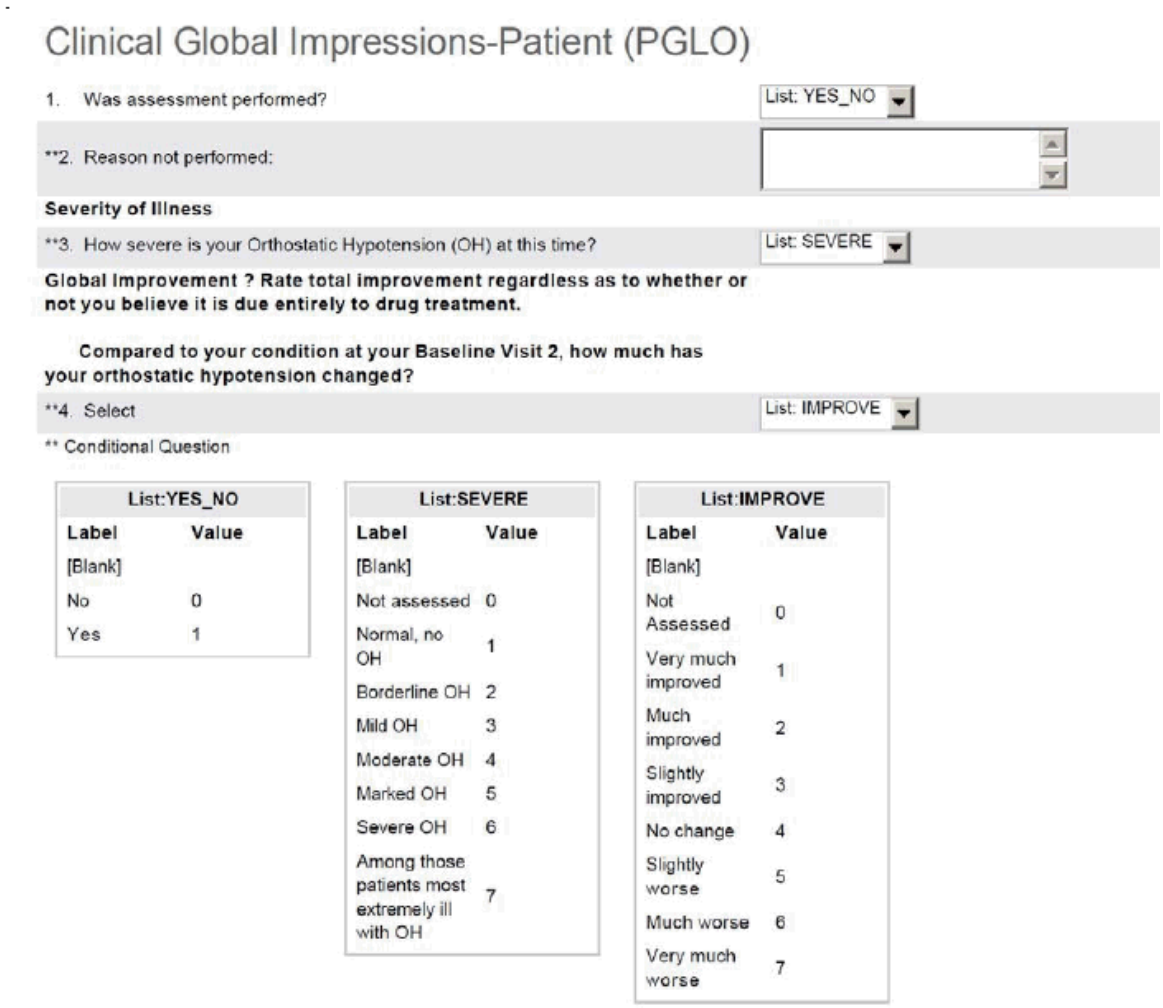
If you cannot do the activity for reasons other than low blood pressure, please check the box at right.

1. Activities that require standing for a short time													**CANNOT DO FOR OTHER REASONS**
No Interference	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**Complete Interference**	☐
2. Activities that require standing for a long time													
No Interference	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**Complete Interference**	☐
3. Activities that require walking for a short time													
No Interference	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**Complete Interference**	☐
4. Activities that require walking for a long time													
No Interference	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**Complete Interference**	☐

9.2.2 The Clinical Global Impression

The Clinical Global Impression-Severity (CGI-S) and Clinical Global Impression-Improvement (CGI-I) scales are global assessment scales. The CGI-S scale assesses the severity of the patient's condition, using a 7 point scale that ranges from 1 (Normal, no OH) to 7 (most extremely ill with OH). The CGI-I scale assesses a patient's improvement relative to baseline and uses a 7 point scale ranging from 1 (very much improved) to 7 (very much worse).

The CGI-S (Severity, question #3) and CGI-I (Improvement, question #4) are listed below, grouped by patient and clinician scoring (source: Clinical review, original submission, 1/27/2012).



Clinical Global Impressions-Patient (PGLO)

1. Was assessment performed? — List: YES_NO

**2. Reason not performed:

Severity of Illness

**3. How severe is your Orthostatic Hypotension (OH) at this time? — List: SEVERE

Global Improvement ? Rate total improvement regardless as to whether or not you believe it is due entirely to drug treatment.

Compared to your condition at your Baseline Visit 2, how much has your orthostatic hypotension changed?

**4. Select — List: IMPROVE

** Conditional Question

List:YES_NO

Label	Value
[Blank]	
No	0
Yes	1

List:SEVERE

Label	Value
[Blank]	
Not assessed	0
Normal, no OH	1
Borderline OH	2
Mild OH	3
Moderate OH	4
Marked OH	5
Severe OH	6
Among those patients most extremely ill with OH	7

List:IMPROVE

Label	Value
[Blank]	
Not Assessed	0
Very much improved	1
Much improved	2
Slightly improved	3
No change	4
Slightly worse	5
Much worse	6
Very much worse	7

Clinical Global Impressions-Clinician (CGLO)

1. Was assessment performed? List: YES_NO

**2. Reason not performed:

Considering your total clinical experience with this particular population, how severe is the patient?s orthostatic hypotension (OH) at this time?

**3. Severity of Illness List: SEVERE

Global Improvement ? Rate total improvement regardless as to whether or not you believe it is due entirely to drug treatment.

Compared to the patient?s Baseline Visit 2 condition, how much has his/her orthostatic hypotension changed?

**4. Global Improvement List: IMPROVE

** Conditional Question

List:YES_NO

Label	Value
[Blank]	
No	0
Yes	1

List:SEVERE

Label	Value
[Blank]	
Not assessed	0
Normal, no OH	1
Borderline OH	2
Mild OH	3
Moderate OH	4
Marked OH	5
Severe OH	6
Among those patients most extremely ill with OH	7

List:IMPROVE

Label	Value
[Blank]	
Not Assessed	0
Very much improved	1
Much improved	2
Slightly improved	3
No change	4
Slightly worse	5
Much worse	6
Very much worse	7

9.2.3 Orthostatic Standing test with standing time:

Table 3 Order and timing of BP, HR measurements and Standing Time

	Supine position			Stand Up (minute 0)	Standing	Standing‡
	-10 min	-5 min	Immediately prior		+3 min*	+10 min (maximum)
Systolic and diastolic BP and HR Measurements	✓	✓	✓	✓	✓	

BP = Blood pressure. HR = Heart rate

* If the investigator considers that a patient cannot, or is unlikely to be able to stand for 3 minutes, blood pressure and heart rate measurements should be taken approximately every 30 seconds (or as frequently as practical). In the event that the patient is unable to stand for 3 minutes, the last blood pressure and heart rate measurements should be recorded in the CRF.

‡ The investigator or their nominated co-worker will monitor and record the total standing time that a patient can stand (up to 10 minutes) and record the standing time on the CRF.

Note: In the supine position, the head and torso were elevated at approximately 30 degrees from horizontal.

Also, the protocol expressly asked investigators not to inform patients as to BP measurements to avoid influencing patient responses; however, patients could be told whether or not their BP measurements were within an acceptable range.

Investigators were also cautioned not to allow observed BP data to influence their assessment of CGI-S and CGI-I for patient status.

9.2.4 Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS):

This instrument has four parts and was included as a safety measure to assess whether droxidopa adversely affects the symptoms and progression of Parkinson's disease.

9.2.5 Parkinson's Disease Questionnaire-39 (PDQ-39):

This thirty-nine item quality of life questionnaire is used to assess the disease from the patient's perspective. The questionnaire provides scores on eight scales: mobility, activities of daily living, emotions, stigma, social support, cognitions, communication and bodily discomfort. The PDQ-39 is included as a safety measure to assess whether droxidopa adversely affects the symptoms and progression of Parkinson's disease.

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/s/

SHARI L TARGUM
12/05/2013

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA Serial Number:	NDA 203-202 (SN 0048)
Drug Name:	Droxidopa
Indication(s):	treatment of symptomatic neurogenic orthostatic hypotension (NOH) in adult patients with primary autonomic failure [Parkinson's Disease (PD), Multiple System Atrophy (MSA) and Pure Autonomic Failure (PAF)], Dopamine Beta Hydroxylase (DβH) Deficiency and Non-Diabetic Autonomic Neuropathy (NDAN)
Applicant:	Chelsea Therapeutics, Inc
Date(s):	Date of Document: August 13, 2013 PDUFA due date: February 13, 2014
Review Priority:	Priority
Biometrics Division:	Biometrics I, HFD-710
Statistical Reviewer:	Jialu Zhang, Ph.D.
Concurring Reviewers:	James Hung, Ph.D.
Medical Division:	Division of Cardiovascular and Renal Products, HFD-110
Clinical Team:	Shari Targum, M.D.
Project Manager:	Anna Park, Pharm.D.

Keywords:

Neurogenic Orthostatic Hypotension, dropout, ANCOVA

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1. EXECUTIVE SUMMARY

The original NDA 203202 was submitted on September 28, 2012 by the sponsor to seek approval of droxidopa in treating symptomatic Neurogenic Orthostatic Hypotension (NOH) associated with Parkinson's disease (PD), Multiple System Atrophy (MSA), Pure Autonomic Failure (PAF), Dopamine Beta Hydroxylase (DBH) deficiency, or Non-Diabetic Autonomic Neuropathy (NDAN). This NDA resubmission included Study 306B to address the deficiencies listed in the Complete Response Letter issued on March 28, 2012.

Study 306B was a multi-center, randomized, parallel-group, placebo-controlled, double-blind study with an initial dose titration, followed by an 8-week treatment period to evaluate the clinical effects of droxidopa in patients with symptomatic Neurogenic Orthostatic Hypotension (NOH) associated with Parkinson's Disease (PD).

After changing the primary endpoint twice, the final primary efficacy endpoint was the mean change in the OHSA Item 1 from Baseline to Week 1. The droxidopa group had a treatment effect of -0.94 compared to the placebo group in the change of OHSA Item 1 score from Baseline to Week 1. The p-value was 0.028 based on ANCOVA model and was statistically significant. Other measurements at Week 1, such as OHQ composite score, clinician and patient reported CGI-I and CGI-S, and standing systolic blood pressure (SBP) were all trending in the right direction, though might not reach statistical significance.

Study 306 went through a number of major changes during its course of conduct including changing the primary endpoint twice, splitting into Study 306A and Study 306B, and changing the total sample size. In addition, it was discovered that the unblinded statistical team had access to the treatment codes for all Study 306 subjects rather than the 51 patients for the interim analysis. Although the access was later revoked, a considerable number of patients in Study 306 were already enrolled. In order to address the concerns on study conduct, the sponsor performed a post-interim sensitivity analysis to show that the study results remained consistent. The reviewer also performed similar analyses at additional time points, such as after revoking access to treatment code and after changing to the final primary endpoint. The treatment effects in various measurements were all trending in the right direction but the magnitude of the treatment effect tended to be less for the patients who enrolled later during the trial.

Although the primary endpoint was statistically significant, the treatment effect on OHSA Item 1 at Week 1 seemed small at the presence of 2.9 unit of intra-subject variability. Also it is questionable whether droxidopa has any long term treatment effect. This was reflected in the diminishing treatment effect on OHSA Item 1 as well as standing SBP in later weeks in the study.

In addition, the imbalance of dropouts between droxidopa group and placebo group was concerning. 20 droxidopa patients were excluded from the primary analysis compared with only 7 placebo patients. Except for three untreated patients, the rest of these patients dropped out early in the study and had missing OHSA Item 1 score at Week 1. Even if excluding 8 patients who

enrolled earlier before the interim analysis, Study 306B still had 4 patients treated with placebo and 12 patients treated with droxidopa discontinued study prior to Week 1. The imbalance remained. The treatment effect on OHSA Item 1 became -0.45 with 95% confidence interval (-1.2, 0.3) if missing data were imputed by carrying forward the baseline observation (BOCF).

2. INTRODUCTION

2.1 Overview

This NDA resubmission included a single phase 3 trial Study 306B. Study 306B was a multi-center, randomized, parallel-group, placebo-controlled, double-blind study with an initial dose titration, followed by an 8-week treatment period to evaluate the clinical effects of droxidopa in patients with symptomatic Neurogenic Orthostatic Hypotension (NOH) associated with Parkinson's Disease (PD).

The trial started as Study 306 and had one interim analysis planned at N=50. The interim analysis was performed on 51 patients who completed 8 weeks of treatment. The DMC recommended terminating the trial due to futility following this interim analysis. After a period of reconsideration, the sponsor decided to continue the study but split the study into Study 306A (which contained 51 unblinded patients used for interim analysis) and Study 306B. The primary endpoint was also changed from OHQ composite score at Week 8 to patient-reported falls at Week 8. The primary endpoint was changed again from patient-reported falls at Week 8 to OHSA 1 at Week 1 after the original NDA was submitted. By then, 122 patients were randomized in Study 306B. Table 1 summarized the two studies included in the NDA resubmission.

Table 1. Efficacy Studies in the NDA Resubmission

Study	Phase and Design	Treatment Period	Follow-up Period	# of Subjects per Arm	Study Population
306B	*Phase 3*	*Up to 2 week titration and 8 weeks of treatment*	*2 weeks*	*85 in placebo and 89 in droxidopa arm*	*Parkinson's Disease*
306A		*Up to 2 week titration and 8 weeks of treatment*	*2 weeks*	*27 in placebo and 24 in droxidopa arm*	*Parkinson's Disease*

The original NDA included three efficacy trials. The pivotal Study 301 was an induction-design trial with a 7-day double-blind randomized treatment period after an open-label dose-titration period and a washout period. The supportive Study 302 was a randomized withdrawal trial with 14-day double-blind randomized withdrawal period. Study 303 was designed to evaluate long-term safety and efficacy of droxidopa by a three-month open-label treatment period followed

with a double-blind randomized withdrawal phase. The NDA was submitted on September 28, 2011. The Division issued a complete response letter on March 28, 2012 stating that "the results of studies 302 and 303 undercut the persuasiveness of study 301" and "the disproportionate contribution of Site 507 to the overall results of study 301 diminishes the persuasiveness of the study". Please refer to the statistical reviews filed in December 2011 and March 2012 for further details.

2.2 Data Sources

The derived analysis datasets and raw datasets for Study 306B can be found under directory \\CDSESUB1\evsprod\NDA203202\0048\m5\datasets\noh306b.

The derived analysis datasets and raw datasets for Study 306A can be found under directory \\CDSESUB1\evsprod\NDA203202\0048\m5\datasets\noh306a

3. STATISTICAL EVALUATION

3.1 Data and Analysis Quality

This NDA resubmission (SN0044) was first submitted on July 3, 2013 and had a number of data-related issues. The division issued an Incomplete Response Letter on July 29, 2013 listing all the data deficiencies, for example, the definition file for 12 raw datasets was missing, and the variable names in analysis datasets used for primary and secondary analyses did not match the variable names in the definition file. The NDA was resubmitted on August 13, 2013. To address the inconsistency of variable names between the datasets and the definition file, the sponsor created new definition files by adding a column with all variable names in the datasets and remapping them to the names in the old definition file. The datasets remained unchanged. However, this did not address the inconsistency of variable names between the SAS programs and the datasets. The so-claimed fully executable programs were not executable due to the inconsistency of variable names.

Nevertheless, the reviewer managed to trace how the primary endpoint was derived. The reviewer was also able to derive same or similar results in most of the primary and secondary analyses results from the CRF raw datasets submitted by the sponsor.

3.2 Evaluation of Efficacy

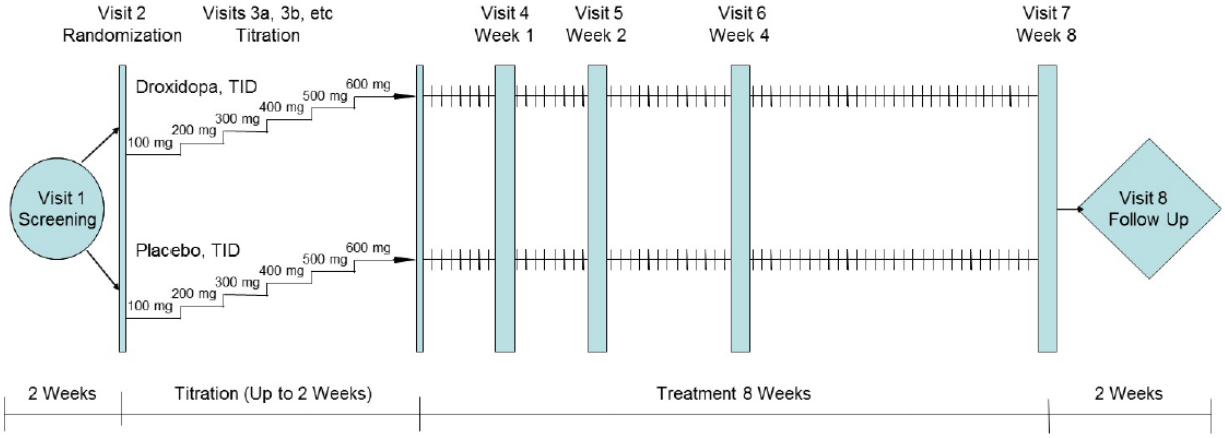
Study Design and Endpoints

Study 306B was a randomized, parallel-group, placebo-controlled, double-blind study with an initial dose titration (up to 14 days), followed by an 8-week treatment period (**Figure 1**). Patients were randomized in a ratio of 1:1 to either droxidopa or placebo at the end of Baseline Visit. Patients then had up to 14 days of double-blind titration starting at 100mg three times daily (TID) of droxidopa or matching placebo. Treatment was escalated in 100 mg TID increments until one of the titration stopping rules was met:

1. The patient became completely asymptomatic for NOH symptoms (clinician-reported CGI-S=1). At the Investigator's discretion, dose escalation may have been stopped when a patient became nearly asymptomatic (clinician-reported CGI-S=2)
2. The patient had a SBP>=180 mmHg or DBP>=110 mmHg after 10 minutes in supine position. At the Investigator's discretion, dose escalation may have been stopped when a patient's BP was close to the limits and further escalation was likely to result in BP levels exceeding the acceptable limit.
3. The patient was unable to tolerate side effects
4. The patient reached a maximum dose of 600 mg TID

Patients who met criterion 1 directly proceeded to the 8-week double-blind treatment period at that dose. Patients who met criterion 2 or 3 proceeded directly to the 8-week treatment period at the previous lower dose. Patients who met criterion 2 or 3 at initial dose of 100 mg TID were withdrawn from treatment. Patient who met criterion 4 continued into the 8-week treatment at 600 mg TID.

Figure 1. Study Design



[Source: Sponsor's clinical study report Figure 9-1]

The primary efficacy endpoint in Study 306B was the mean change in the OHSA Item 1 score from Baseline to Week 1. **The primary endpoint was changed twice during the trial**. The trial started as Study 306 and it was designed to measure the long-term safety and efficacy of droxidopa. The original primary endpoint was the mean change in OHQ composite score from Baseline to Week 8. An interim analysis was planned to assess study sample size at N=50. The actual interim analysis was performed when 51 patients completed 8-week treatment. The DMC recommended terminating the trial due to futility in January 2011 following the interim analysis. After a period of reconsideration, the sponsor decided to continue the study and changed the primary endpoint to patient-reported falls at Week 8. To maintain study integrity, the study was split to Study 306A (which contained 51 unblinded patients used for interim analysis) and Study 306B. The primary endpoint was changed again from patient-reported falls to OHSA Item 1 score at Week 1 in November 2011. The change was reflected in protocol version 4 dated November 5, 2011. By then, 122 patients were randomized in Study 306B. A total of 174 patients were enrolled into Study 306B and the last patient enrolled on August 10, 2012.

The sponsor planned to have 200 patients (100 patients each arm) when the primary endpoint was patient-reported falls. According to protocol version 4, this would provide 80% power to detect a treatment difference of 0.5 in patient-reported falls. The decision on terminating the study was announced in July 2012 and the total number of patients enrolled in the study was 174 (85 in placebo and 89 in droxidopa). The sponsor claimed that the trial was prematurely stopped based in FDA Advice Letter dated June 29, 2012. The letter expressed concerns that it was "not possible to know with certainty that interim results did not somehow influence decisions to change the primary efficacy endpoint of study 306". On the other hand, it was not clear to the reviewer whether the sponsor intended to keep the same sample size after changing the primary endpoint to OHSA Item 1 at week 1. The only protocol that reflect the change on the final primary endpoint OHSA Item 1 (version 5) was dated on November 2, 2012, which was after the last patient completed the study (October 23, 2012). The final SAP was dated on October 4, 2012 and was also after the enrollment was stopped.

The secondary efficacy variables in Study 306B were:

- The mean change in OHSA Item #1 from Baseline to week 2 (Visit 5)
- The mean change in OHSA Item #1 from Baseline to week 4 (Visit 6)
- The mean change in the lowest standing systolic blood pressure between 0 and +3 minutes of standing from Baseline to week 1 (Visit 4)
- The mean change in OHSA Item #1 from Baseline to week 8 (Visit 7)
- Rate of patient reported falls from Baseline to the end of the study (FAS)
- The mean change in OHQ from Baseline to week 8 (Visit 7)

The secondary endpoints were tested sequentially in the order listed above if the primary efficacy endpoint won at significance level of 0.05.

Patient Disposition, Demographic and Baseline Characteristics

A total of 174 patients were randomized in Study 306B (89 patients in droxidopa and 85 patients in placebo). 28% droxidopa patients discontinued study early compared to 20% placebo patients (**Table 2**).

Table 2. Patient Disposition

	Placebo (N=85) n (%)	Droxidopa (N=89) n (%)	Total (n=174) n (%)
Total Patients Randomized	85 (100)	89 (100)	174 (100)
Total Patients Treated	84 (98.8)	87 (97.8)	171 (98.3)
Completed Study	67 (78.8)	62 (69.7)	129 (74.1)
Discontinued Study	17 (20.0)	25 (28.1)	42 (24.1)
Reason for Discontinuation			
Treatment Failure	1 (1.2)	1 (1.1)	2 (1.1)
Adverse Event	6 (7.1)	10 (11.2)	16 (9.2)
Lack of Efficacy	2 (2.4)	4 (4.5)	6 (3.4)
Protocol Violation	0	1 (1.1)	1 (0.6)
Lost to Follow Up	1 (1.2)	0	1 (0.6)
Patient Withdrew Consent	1 (1.2)	3 (3.4)	4 (2.3)
Investigator Decision	1 (1.2)	2 (2.2)	3 (1.7)
Other	5 (5.9)	4 (4.5)	9 (5.2)

[Source: Sponsor's Clinical Study Report Table 10-1, verified by the reviewer]

Table 3 listed the three analysis populations. The Safety Set consisted of all patients who received at least one dose of study drug. The Full Analysis Set (FAS) was the population used for the primary analysis and consisted of all randomized patients who received at least one dose of study drug and reported OHSA Item 1 data at Week 1. Only 69 patients in droxidopa group were included in the primary analysis compared to 78 patients in placebo.

The Per Protocol Set consisted of patients in the FAS who were compliant with study treatment. Patients must have taken at least 80% of their planned study drug during the first four weeks of the treatment period and during the final four weeks of the treatment period.

Table 3. Analysis Populations

	Placebo (N=85)	Droxidopa (N=89)	Total (n=174)
Analysis Populations			
Safety Set	82 (96.5)	89 (100.0)	171 (98.3)
Full Analysis Set	78 (91.8)	69 (77.5)	147 (84.5)
Per Protocol Set	45 (52.9)	34 (38.2)	79 (45.4)

[Source: Sponsor's Clinical Study Report Table 11-1, verified by the reviewer]

The majority of patients in both treatment groups were male (69.7% in droxidopa group and 63.4% in placebo group). The mean ages were 72.5 years and 72.0 years for patients in the droxidopa and placebo groups, respectively. Most patients were White (95.5% in droxidopa group and 96.3% in placebo group). All patients were enrolled in the US.

Table 4. Demographic and Baseline Characteristics (Safety Set)

	Placebo (N=82)	Droxidopa (N=89)
Sex [n (%)]		
Male	52 (63.4)	62 (69.7)
Female	30 (36.6)	27 (30.3)
Race [n (%)]		
White	79 (96.3)	85 (95.5)
Black/African American	1 (1.2)	2 (2.2)
Asian	0	1 (1.1)
Hispanic/Latino	2 (2.4)	1 (1.1)
Age (Years) at Screening		
Mean (SD)	72.01 (8.036)	72.54 (7.571)
Min, Max	52.9, 86.3	41.4, 91.7
Weight (kg)		
Mean (SD)	77.06 (15.913)	78.03 (17.002)
Min, Max	45.5, 122.3	46.4, 122.0

[Source: Sponsor's clinical study report Table 11-2, verified by the reviewer]

Statistical Methodologies

The primary efficacy analysis was based on the Full Analysis Set. According to the sponsor's final SAP, the primary endpoint would be tested using analysis of covariance (ANCOVA) model adjusting for Baseline OHSA Item 1 score. However, if any of the ANCOVA assumptions (independence, constant variance or normality of the residuals) were not met then the primary analysis would be changed to non-parametric model using rank statistics adjusted for the OHSA Item 1 at Baseline. The violation of assumptions was determined by visually inspecting the diagnostic plots and no formal test was proposed.

The analysis of patient-reported falls was performed for all subjects' data in the FAS and included all data while subjects were in the study. The other secondary efficacy endpoints were analyzed with missing data excluded. LOCF was used as a sensitivity analysis.

Results and Conclusions

The sponsor reported that the assumptions for the ANCOVA were not met and used non-parametric methodology instead for the primary analysis. The resulting p-value was 0.018 and the treatment difference in OHSA Item 1 score was -1.0 with 95% confidence interval (-2.0, 0). The reviewer, however, did not find any obvious deviation from ANCOVA assumptions. Table 5 summarized the reviewer's results on primary endpoint by ANCOVA. The droxidopa group had a treatment effect of -0.94 when compared to placebo group in terms of change in OHSA Item 1 score from Baseline to Week 1. The p-value was 0.028 and was statistically significant.

Table 5. Primary Endpoint Results

	Droxidopa			Placebo		
	N	Mean	STD	N	Mean	STD
Baseline	69	5.1	2.04	78	5.1	2.33
Week 1	69	2.8	2.44	78	3.8	2.75
Least square mean difference	-0.94 with 95% CI (-1.78, -0.1)					
p-value from ANCOVA model	0.028					

Figure 2 showed the cumulative distribution of the change in the OHSA Item 1 score from Baseline to Week 1. **Figure 3** displayed the relationship between the baseline OHSA Item 1 score and the change in the OHSA Item 1 score from Baseline to Week 1. The two parallel lines are the estimated values of the change in OHSA 1 from Baseline in placebo group (blue) and in droxidopa group (grey) from the ANCOVA model in the primary analysis. The magnitude of change in the OHSA Item 1 from Baseline to Week 1 had a strong linear relationship with the baseline OHSA Item 1. The variability also seemed large. The intra-subject variability was 2.9. The reviewer calculated the intra-subject variability by including only the post-baseline visits (Week 1, Week 2, Week 4 and Week 8). Although the treatment effect on OHSA Item 1 at Week 1 reached statistical significance, the magnitude of the treatment effect (1 unit) seemed small when compared to the intra-subject variability.

Figure 2. Cumulative Distribution on the Change of OHSA Item 1 from Baseline at Week 1

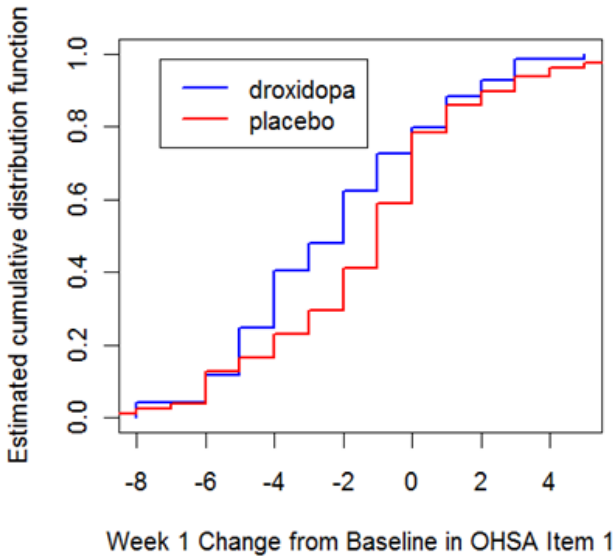
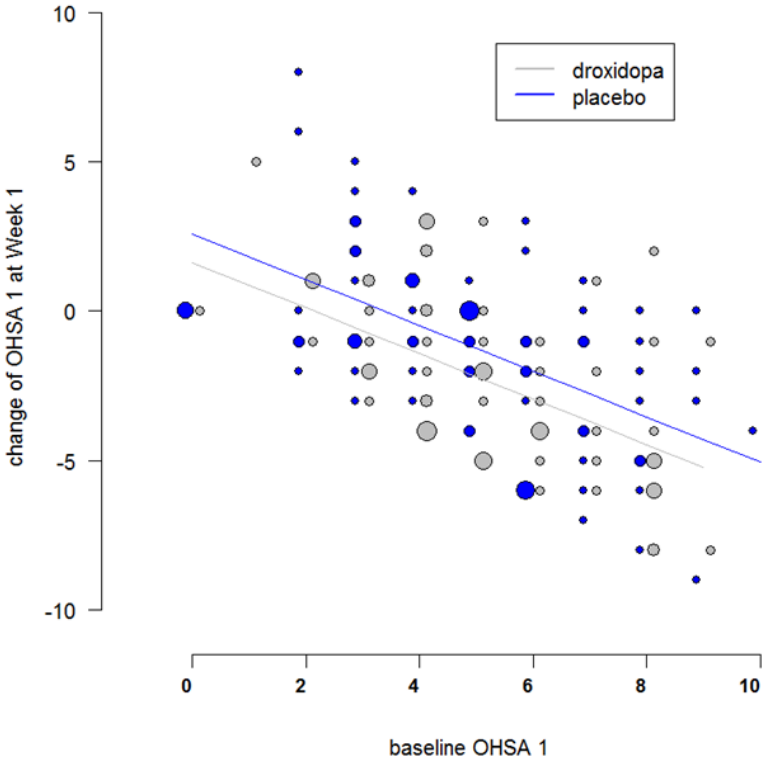


Figure 3. Change of OHSA 1 at Week 1 versus Baseline OHSA 1



* bigger circle represents larger number of patients

Sponsor also performed other analyses on the primary endpoint, for example, the responder's analysis. Significantly more patients had big improvement (>=4 unit improvement in OHSA 1) in droxidopa group compared with placebo group in the responder's analysis (Table 6).

Table 6. Responder's Analysis on OHSA 1 at Week 1

	OHSA Item 1 Unit Improvements		
	Placebo (N=78) N (%)	Droxidopa (N=69) N (%)	P-value
≥1 Unit Improvement from Baseline			0.118
Yes	46 (59.0)	50 (72.5)	
No	32 (41.0)	19 (27.5)	
≥2 Unit Improvement from Baseline			0.013
Yes	32 (41.0)	43 (62.3)	
No	46 (59.0)	26 (37.7)	
≥3 Unit Improvement from Baseline			0.027
Yes	23 (29.5)	33 (47.8)	
No	55 (70.5)	36 (52.2)	
≥4 Unit Improvement from Baseline			0.032
Yes	18 (23.1)	28 (40.6)	
No	60 (76.9)	41 (59.4)	

[Source: Sponsor's Clinical Study Report Table 11-6, verified by the reviewer]

The primary analysis used Full Analysis Set, which consisted of patients who took at least one dose of study drug and had OHSA Item 1 score at Week 1. 20 patients randomized to droxidopa were excluded from the primary analysis and only 7 patients in placebo were excluded. Droxidopa group had more dropouts during the titration phase. Table 7 listed the dropout reasons for these patients. Among treated patients, 6 placebo patients and 18 droxidopa patients discontinued study before Week 1.

Table 7. Discontinuation Reason for Patients Excluded from Full Analysis Set

Discontinuation Reason	Placebo	Droxidopa
Not treated	1	2
Treatment Failure	0	1
Adverse Event	4	6
Lack of Efficacy	0	3
Protocol Violation	0	1
Patient Withdrew Consent	0	3
Investigator Decision	0	2
Other	2	2
Total	7	20

The sponsor argued that the patient discontinuation rate was inflated in 306B. The interim analysis for 306 only included the patients who completed titration phase and finished the study. So patients who enrolled early but discontinued the study prior to completing titration were not included in the interim analysis. A total of 8 patients enrolled in the trial and dropped out during titration phase prior to the interim cut-off date. They were excluded from interim analysis and therefore were included in Study 306B. 7 out of the 8 patients were in droxidopa group. But even by excluding these 8 patients, Study 306B still had 5 placebo patients and 11 droxidopa patients who discontinued study prior to Week 1. The imbalance remained. In addition, one of the five placebo patients was treated with droxidopa although the planned treatment was placebo. So 4 patients treated with placebo and 12 patients treated with droxidopa discontinued study prior to Week 1. In fact, both patients enrolled earlier and patients enrolled later in the study showed similar pattern that droxidopa group had more dropouts.

Since OHSA Item 1 score was not measured during titration phase, patients with missing OHSA Item 1 at Week 1 only had baseline OHSA Item 1 score. One simple way to impute the missing data was to carry forward the baseline observations. The treatment effect was -0.45 with 95% confidence interval (-1.2, 0.3). This is not surprising since droxidopa group had more missing data and the imputation would bring more zeros to the droxidopa group.

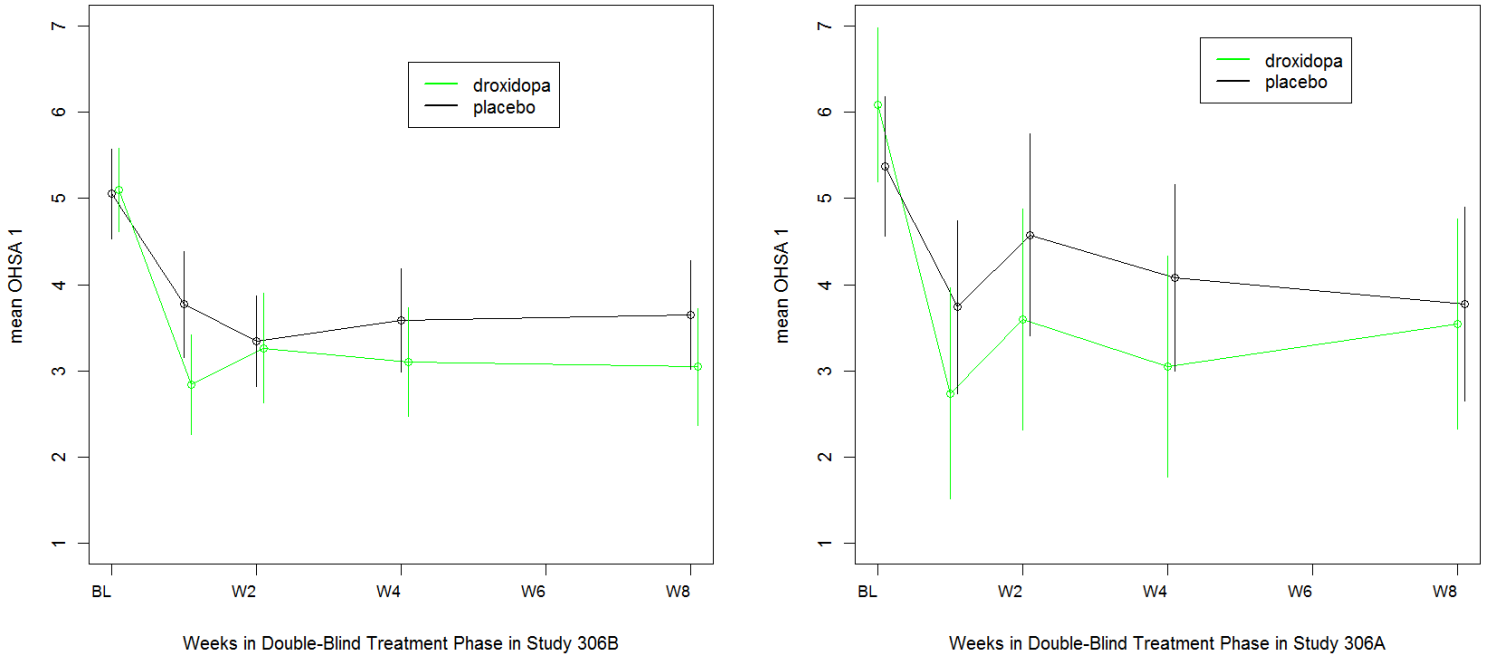
The reviewer examined the durability of the treatment effect on OHSA Item 1 by looking at its change from Baseline to Weeks 2, 4 and 8 (Table 8 and Figure 4). The treatment effect on OHSA Item 1 almost completely diminished at Week 2 and the treatment effect in Week 4 and Week 8 were also less than in Week 1.

Figure 5 and **Figure 6** displayed OHQ composite score and standing SBP (lowest between 0 and 3 minutes of standing in 306B, 3 minutes of standing in 306A) by visit. Study 306A showed almost no effect in OHQ composite score, which was the reason that DMC recommended terminating the trial for futility in 2011. Depending on the visits, the treatment effect in change of OHQ composite score varied between 0.4 to 0.7 unit in Study 306B (Table 12). The standing systolic blood pressure (lowest between 0 and +3 minutes of standing) had 5.4 mmHg more increase in change from Baseline to Week 1 in droxidopa group when compared with placebo. The treatment effect, however, did not seem to sustain through the 8-week treatment period for both Study 306A and Study 306B (**Table 13**). It is questionable whether droxidopa has any long-term clinical benefits.

Table 8. Summary on OHSA Item 1 Score at Weeks 2, 4 and 8

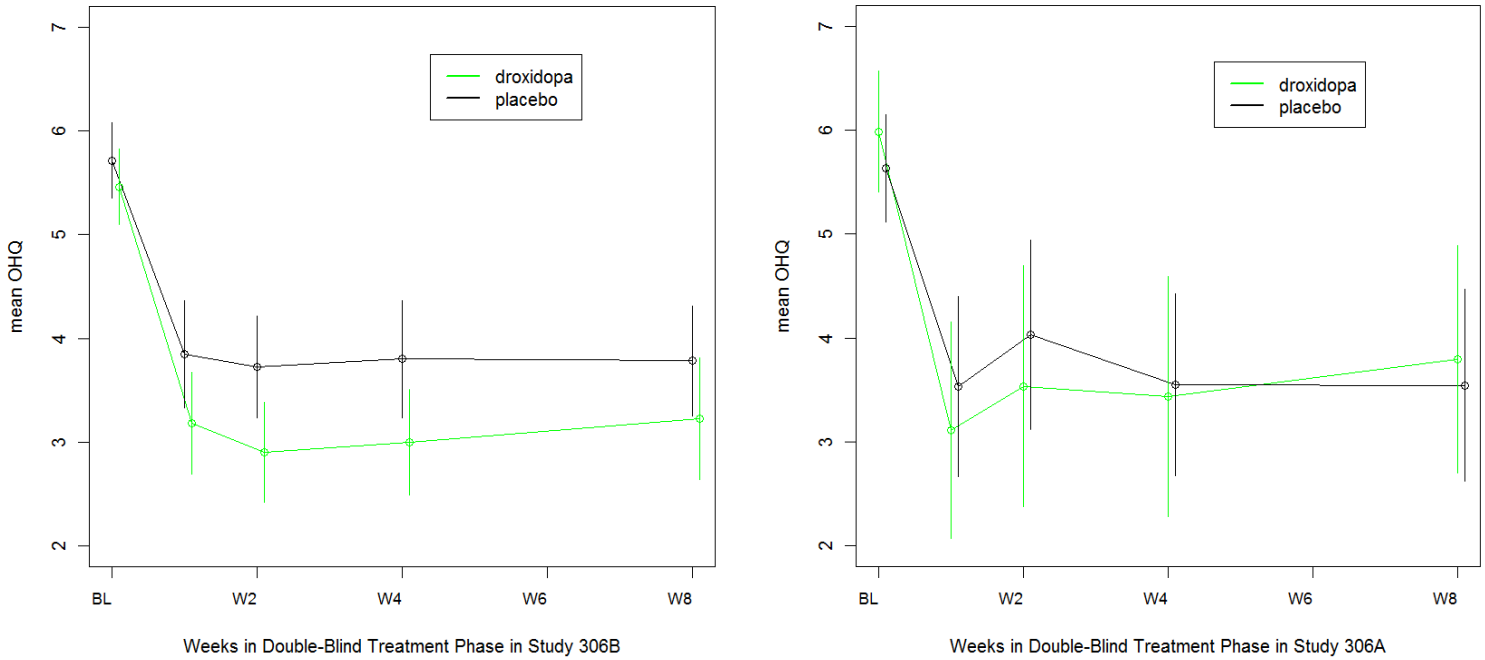
	Droxidopa			Placebo		
	N	Mean	STD	N	Mean	STD
Week 2	68	3.3	2.69	75	3.3	2.32
Change from Baseline to Week 2	68	-1.9	2.86	75	-1.6	2.97
Least square mean difference	-0.12 with 95% CI (-0.93, 0.69)					
p-value from ANCOVA	0.77					
Week 4	67	3.1	2.64	73	3.6	2.6
Change from Baseline to Week 4	67	-2	3.08	73	-1.5	2.74
Least square mean difference	-0.5 with 95% CI (-1.33, 0.36)					
p-value from ANCOVA	0.26					
Week 8	63	3	2.75	68	3.6	2.64
Change from Baseline to Week 8	63	-2.1	3.03	68	-1.5	2.91
Least square mean difference	-0.6 with 95% CI (-1.49, 0.30)					
p-value from ANCOVA	0.19					

Figure 4. OHSA 1 by Visit



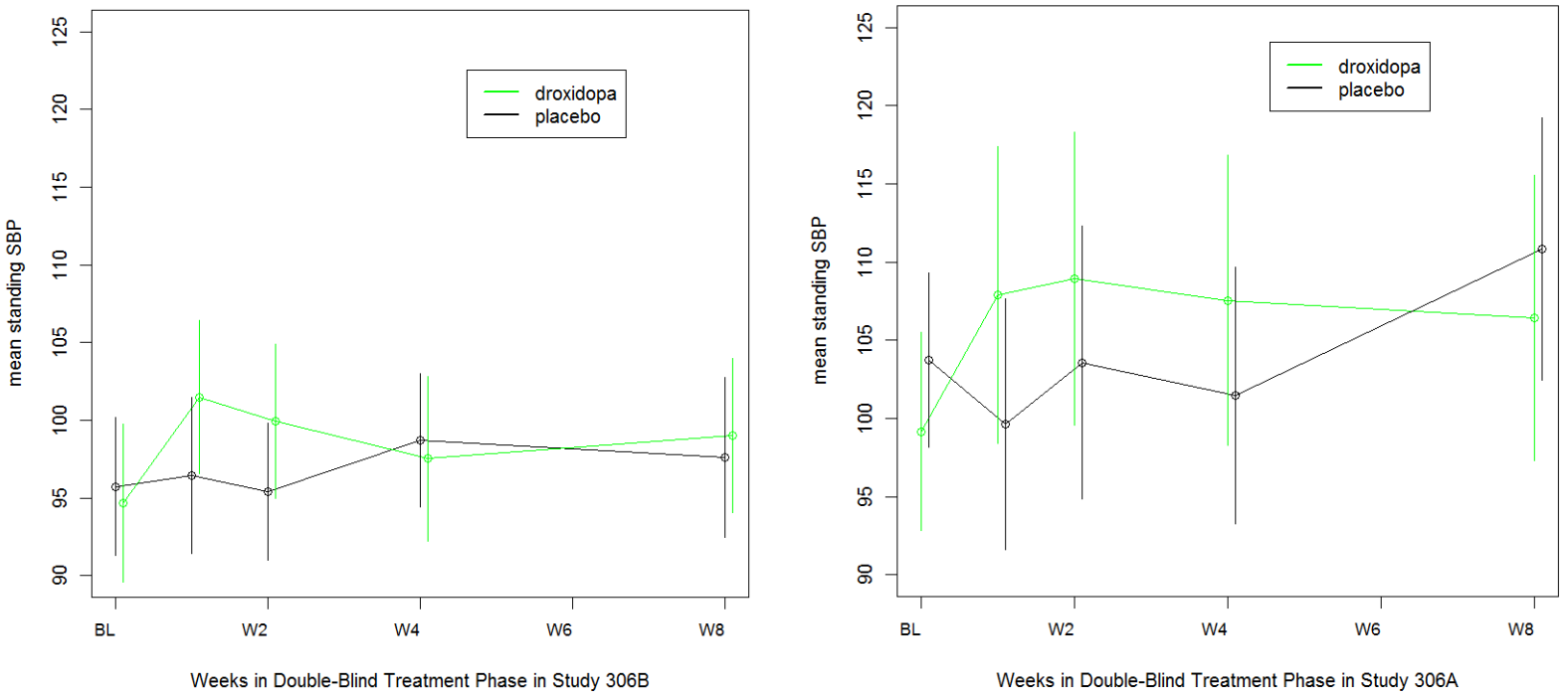
* left side is the mean OHSA Item 1 score by visit in each treatment group in Study 306B, right side is the mean OHSA Item 1 score by visit in each treatment group in Study 306A. Vertical lines are the 95% confidence interval of the mean OHSA Item 1 score for each individual treatment group at each specific visit

Figure 5. OHQ by Week



* left side is the mean OHQ composite score by visit in each treatment group in Study 306B, right side is the mean OHQ composite score by visit in each treatment group in Study 306A. Vertical lines are the 95% confidence interval of the mean OHQ composite score for each individual treatment group at each specific visit

Figure 6. Standing SBP by Week



* left side is the mean of the lowest standing SBP between 0 and +3 minutes of standing by visit in each treatment group in Study 306B, right side is the mean of standing SBP at 3 minutes of standing by visit in each treatment group in Study 306A. Vertical lines are the 95% confidence interval of the mean standing SBP for each individual treatment group at each specific visit

Patient-reported fall was once the primary endpoint. The sponsor showed that in Study 306B droxidopa patients experienced a lower total number of falls during the treatment period when compared with placebo patients (**Table 9**). By further examining the data, the reviewer noticed that patient 122013 and patient 146007 in placebo group had 118 and 358 reported falls, respectively. If excluding the two patients, the total number of falls in placebo group reduced to 240 compared with 229 reported falls in droxidopa group. The treatment difference in the total number of falls disappeared.

Table 9. Summary on Patient-Reported Falls

Analysis	Placebo (N=78)[2]	Droxidopa (N=69)[1]
Total Number of Falls, n	716	229
Percentage of Patients with ≥1 Fall[3], n (%)	47 (60.3)	40 (58.0)
Mean Patient Rate of Falls Per Patient-Week[4]	2.0 (12.95)	0.4 (0.84)

[Source: Sponsor's clinical study report Table 11-11, verified by the reviewer]

Study 306 went through a number of major changes during its course of conduct including changing the primary endpoint twice, splitting into Study 306A and Study 306B, changing sample size, and discovering inappropriate access to the treatment code for all study patients. **Table 10** summarized the chronicle of Study 306. The division had concerns over a number of major changes on the study design, especially towards the end of the study, which would undermine the creditability of the study results. Although the sponsor provided documents on their blinding process, it was impossible to be aware of every non-electronic communication occurred.

The sponsor also performed a post-interim sensitivity analysis on efficacy endpoints that included 121 patients to show that the post-interim results were consistent with the whole study. Based on the order of enrollment date, the Post-interim Analysis Set would include all FAS patients who were randomized after November 10, 2010. The cutoff date for the interim analysis, however, was December 14, 2010. Since maintaining treatment blinding was the concern, every patient who was randomized before the conduct of interim analysis should be excluded for sensitivity analysis.

So reviewer performed a similar post-interim analysis by including only patients who were randomized after December 14, 2010. A total of 113 patients were included in the reviewer's analysis. The results were similar to the sponsor's results on 121 patients and were consistent with the whole population (**Table 11**). The reviewer also performed similar subset analysis at different time points to further examine the data consistency. The treatment effects in various measurements were all trending in the right direction but the magnitude of the treatment effect tended to be less for the patients who enrolled later during the trial. For example, the estimate on the change in OHSA Item 1 score from Baseline to Week 1 was 0.6 by excluding all patients who were randomized before the inappropriate access to treatment code was revoked.

An interesting finding was that the treatment effect in the patient-reported CGI-I always was less than in the clinician-reported CGI-I (**Table 11**), which may be an indication of bias on one of the measurements.

Table 10. Timeline on Major Events

Date	Event
March 10, 2010	Study 306 protocol version 1: total sample size was at least 84. Primary endpoint was OHQ composite score at Week 8. The study was multi-national and it had no interim analysis
September 1, 2010	Study 306 protocol version 2: The study was changed to US only
November 19, 2010	Study 306 protocol version 3: Interim analysis at 60% information time (N=50) was added to re-assess treatment effect. This may result in sample size increase up to a maximum of 192
December 14, 2010	Cut-off date for 306 interim analysis. 94 patients were enrolled. The analysis included the first 51 patients who completed End of Study visit. PPD extraction Team extracted data from 92 patients into a Blinded Project Area where the unblinded DMC team have access
January 25, 2011	DMC met and recommended to stop Study 306 due to futility. 113 patients were enrolled into the study
February 9, 2011	PPD informed Chelsea that the unblinded statistical team may have been provided with access to the randomization codes for all Study 306 subjects.
February 23, 2011	Enrollment resumed for Study 306
March 2, 2011	PPD confirmed that unblinded statistical team did have access to the treatment code for all 306 subjects. The access was revoked. 118 patients were enrolled in the study by now.
April 11, 2011	FDA advised on protocol amendment submitted on March 16, 2011 that "Study NOH306B will not be accepted by the Division as supportive of efficacy"
May 12, 2011	Study 306 protocol version 4: The primary endpoint was changed to difference in patient reported falls at Week 8. The study was split into Study 306A (N=51) and Study 306B (N=160). No interim analysis was planned for Study 306B.
September 28, 2011	Chelsea submitted NDA including Study 301 and Study 302
November 5, 2011	Study 306 protocol version 5: The primary endpoint was changed to OHSA Item 1 at Week 1 for Study 306B and sample size was increased to 200
March 28, 2012	Complete response letter was issued
May 10, 2012	159 patients enrolled in Study 306B
May 31, 2012	Chelsea proposed to use Study 306B to fulfill FDA's requirement for additional confirmatory trial

June 29, 2012	FDA expressed concern on Study 306B, stating that it is impossible to know with certainty that interim results did not influence decisions to change the primary endpoint of Study 306B
August 10, 2012	Last patient enrolled in Study 306B. The sponsor announced to stop patient enrollment in July 2012.

Table 11. Comparison of Efficacy Results at Different Time Point

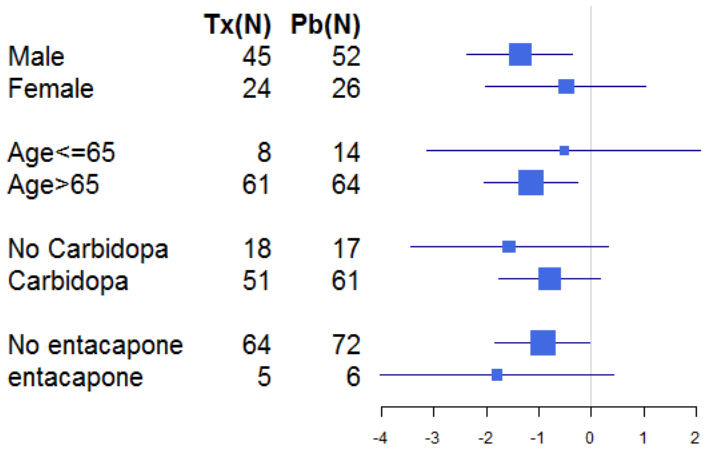
	Whole Study Population		Sponsor's Post Interim Analysis		Reviewer's Post Interim Analysis		Revoking Access to Treatment Code		Changing Primary Endpoint	
			After Nov 10, 2010		After Dec 14, 2010		After March 2, 2011		After May 12, 2011	
	N=147		N=121		N=113		N=93		N=71	
	trt eff est	CI	trt eff est	CI	trt eff est	CI	trt eff est	CI	trt eff est	CI
OHSA Item 1: Mean change from baseline at Week 1	-0.9	(-1.8, 0.1)	-1.1	(-2.0, -0.1)	-1.0	(-2.0, -0.05)	-0.6	(-1.7, 0.5)	-0.7	(-2.0, 0.6)
Lowest standing SBP between 0 to 3 minutes at Week 1	5.4	(-0.5, 11.3)	5.8	(-0.9, 12.4)	5.0	(-2.0, 12.0)	2.5	(-5.0, 10.0)	0.8	(-8.5, 10.1)
OHQ mean change from baseline at Week 1	-0.6	(-1.2, 0.1)	-0.7	(-1.5, 0.03)	-0.7	(-1.4, 0.1)	-0.4	(-1.2, 0.4)	-0.3	(-1.3, 0.7)
Clinician-reported CGI-S at Week 1	-0.4	(-0.8, -0.05)	-0.5	(-0.9, -0.1)	-0.5	(-0.9, -0.1)	-0.4	(-0.9, 0.03)	-0.2	(-0.7, 0.3)
Patient-reported CGI-S at Week 1	-0.4	(-0.8, 0.02)	-0.5	(-0.9, -0.04)	-0.5	(-0.9, -0.02)	-0.4	(-1.0, 0.1)	-0.2	(-0.8, 0.4)
Clinician-reported CGI-I at Week 1	-0.5	(-0.9, -0.1)	-0.6	(-1.0, -0.2)	-0.7	(-1.1, -0.2)	-0.5	(-1.0, -0.1)	-0.4	(-1.0, 0.1)
Patient-reported CGI-I at Week 1	-0.2	(-0.5, 0.1)	-0.3	(-0.7, 0.01)	-0.3	(-0.7, 0.02)	-0.2	(-0.6, 0.2)	-0.2	(-0.7, 0.3)

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

The population for Study 306B was predominantly white and all patients were enrolled in US. Therefore, no subgroup analyses on race and country were performed. Figure 7 showed results of some subgroup analyses.

Figure 7. Forest Plot on Subgroup Analyses



4.2 Other Special/Subgroup Populations

The reviewer specifically examined patients by whether they took entacapone or not and whether they took carbidopa/levodopa (Sinemet) since carbidopa and entacapone may modify the metabolism of droxidopa. The results were showed in the forest plot (Figure 7).

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

After changing the primary endpoint twice, the final primary efficacy endpoint was the mean change in the OHSA Item 1 from Baseline to Week 1. The sponsor concluded that the assumptions for the ANCOVA were not met and used non-parametric methodology for the primary analysis. Based on the sponsor's analysis, the droxidopa group had a treatment effect of

-1 with 95% confidence interval (-2.0, 0) when compared to placebo group in change of OHSA Item 1 score from Baseline to Week 1 and the p-value was 0.018. The reviewer, however, did not find any obvious deviation from ANCOVA assumptions. The treatment effect based on ANCOVA model was -0.94 and the p-value was 0.028. Both results were statistically significant.

Although statistically significant, the treatment effect on OHSA Item 1 at Week 1 seemed small at the presence of intra-subject variability, which was 2.9 based on reviewer's calculation.

The treatment effect at later weeks in the study was not so consistent. The treatment effect on OHSA Item 1 almost completely diminished at Week 2 and was also less at Week 4 and Week 8. The treatment effect in standing SBP did not sustain through the 8-week treatment period. This made it questionable whether droxidopa has any long term treatment effect.

Study 306 went through a number of major changes during its course of conduct including changing the primary endpoint twice, splitting into Study 306A and Study 306B, and changing the total sample size. In addition, it was discovered that the unblinded statistical team had access to the treatment codes for all Study 306 subjects rather than the 51 patients for the interim analysis. Although the access was later revoked, a considerable number of patients in Study 306 were already enrolled. In order to address the concerns on study conduct, the sponsor performed a post-interim sensitivity analysis to show that the study results remained consistent. The reviewer also performed similar analyses at additional time points, such as after revoking the access to treatment code and after changing to the final primary endpoint. The treatment effects in various measurements were all trending in the right direction but the magnitude of the treatment effect tended to be less for the patients who enrolled later during the trial.

Droxidopa group had more dropouts during the titration phase. 20 droxidopa patients were excluded from the primary analysis compared with only 7 placebo patients. Except for three untreated patients, the rest of these patients had missing OHSA Item 1 score at Week 1. Even if excluding 8 patients who enrolled earlier before the interim analysis, Study 306B still had 4 patients treated with placebo and 12 patients treated with droxidopa discontinued study prior to Week 1. The imbalance remained. It is concerning to see such imbalance of dropouts between treatment groups, especially if the data were not missing at random. The treatment effect of OHSA Item 1 became -0.45 with 95% confidence interval (-1.2, 0.3) if imputing missing data by carrying forward baseline observation (BOCF).

5.2 Conclusions and Recommendations

The droxidopa group had a statistically significant treatment effect over placebo group in the mean change in the OHSA Item 1 score from Baseline to Week 1. Other measurements at Week 1 were all trending in the right direction, though might not reach statistical significance.

However, the treatment effect on OHSA Item 1 at Week 1 seemed small when compared with intra-subject variability. It is also concerning to observe an imbalance of dropouts between treatment groups. The treatment effect of droxidopa did not seem to sustain through the 8-week

treatment period. This made it questionable whether droxidopa has any long term treatment effect.

The credibility of the study was also undermined by a number of major changes on the study design and the discovery of inappropriate access to the treatment codes of all study patients enrolled until March 2011. Sensitivity analyses were performed to include only patients enrolled after certain time point to examine the consistency of the study results. The treatment effects in various measurements were all trending in the right direction but the magnitude of the treatment effect tended to be less for the patients who enrolled later during the trial.

Overall, Study 306B alone did not seem to provide strong and robust evidence to support the efficacy of droxidopa in treating NOH, especially for long-term treatment.

APPENDIX

Table 12. Summary on OHQ Composite Score by Visit

	Droxidopa			Placebo		
	N	Mean	STD	N	Mean	STD
Baseline	69	5.5	1.54	78	5.7	1.64
Week 1	69	3.2	2.07	78	3.9	2.33
Change from Baseline to Week 1	69	-2.3	2.12	78	-1.9	2.39
Least square mean difference	-0.55 with 95% CI (-1.24, 0.14)					
p-value from ANCOVA	0.115					
Week 2	68	2.9	2.03	75	3.7	2.17
Change from Baseline to Week 2	68	-2.5	1.98	75	-2	2.26
Least square mean difference	-0.71 with 95% CI (-1.37, -0.06)					
p-value from ANCOVA	0.032					
Week 4	67	3	2.12	73	3.8	2.46
Change from Baseline to Week 4	67	-2.5	1.93	73	-1.9	2.28
Least square mean difference	-0.64 with 95% CI (-1.33, 0.05)					
p-value from ANCOVA	0.068					
Week 8	63	3.2	2.38	68	3.8	2.23
Change from Baseline to Week 8	63	-2.2	2.29	68	-2	2.18
Least square mean difference	-0.40 with 95% CI (-1.14, 0.38)					
p-value from ANCOVA	0.29					

Table 13. Summary on Standing SBP by Visit

	Droxidopa			Placebo		
	N	Mean	STD	N	Mean	STD
Baseline	69	94.7	21.5	78	95.7	20.1
Week 1	68	101.5	20.8	78	96.4	22.7
Change from Baseline to Week 1	68	6.4	18.9	78	0.7	20.2
Least square mean difference	5.4 with 95% CI (-0.5, 11.3)					
p-value from ANCOVA	0.07					
Week 2	68	99.9	20.9	75	95.4	19.6
Change from Baseline to Week 2	68	5.5	19.3	75	-0.6	20.3
Least square mean difference	5.4 with 95% CI (-0.3, 11.0)					
p-value from ANCOVA	0.06					
Week 4	65	97.5	21.9	73	98.7	18.7
Change from Baseline to Week 4	65	2.8	20.2	73	3	19.4
Least square mean difference	-0.7 with 95% CI (-6.4, 5.1)					
p-value from ANCOVA	0.82					
Week 8	64	99	20.3	69	97.6	21.8
Change from Baseline to Week 8	64	5	18.5	69	0.9	18.4
Least square mean difference	3.0 with 95% CI (-2.7, 8.8)					
p-value from ANCOVA	0.29					

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/s/

JIALU ZHANG
12/03/2013

HSIEN MING J HUNG
12/03/2013

CLINICAL PHARMACOLOGY REVIEW

NDA:	203202
Submission Date:	08/14/2013
Submission Type:	NME, Re-submission, Priority Review
Brand Name:	NORTHERA®
Generic Name:	Droxidopa
Dosage Form & Strengths:	Capsules: 100, 200 and 300 mg
Proposed Indication:	For the treatment of symptomatic neurogenic orthostatic hypotension in adult patients with primary autonomic failure (Parkinson's Disease, Multiple System Atrophy and Pure Autonomic failure), Dopamine Beta Hydroxylase Deficiency and Non-Diabetic Autonomic Neuropathy
Applicant:	Chelsea Therapeutics
Review Divisions:	DCRP & DCP1
Primary Reviewer:	Sreedharan Sabarinath, Ph.D.
Team Leaders:	Yaning Wang, Ph.D. Rajanikanth Madabushi, Ph.D.

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EXECUTIVE SUMMARY

Chelsea Therapeutics, Inc. had an original new drug application (NDA 203-202, submission date 09/03/2011) for droxidopa capsules for the treatment of symptomatic neurogenic orthostatic hypotension (NOH) in adult patients with primary autonomic failure (Parkinson's disease, Multiple System Atrophy and Pure Autonomic Failure), Dopamine Beta Hydroxylase Deficiency and Non-Diabetic Autonomic Neuropathy. This original NDA received a complete response (CR) after a priority review and an advisory committee meeting (CR letter date 03/28/2012). Original clinical pharmacology question based review (QBR) and individual study reviews were completed in the first review cycle and are available in DARRTS (dates 01/25/2012 and 03/18/2012). The current re-submission includes one pivotal efficacy study (306B) and a bioequivalence study (104) for a new 300 mg capsule strength.

The pivotal efficacy study 306B was in adult patients with symptomatic neurogenic orthostatic hypotension (NOH) associated with Parkinson's disease and had parallel treatment arms with droxidopa and matching placebo with an initial double-blind dose-titration phase followed by an 8-week maintenance phase. Study 306B showed a treatment effect of 1.0 unit (p=0.018) favoring droxidopa for the primary efficacy endpoint (placebo adjusted change from baseline to week 1 for Orthostatic Hypotension Symptom Assessment, OHSA, Item-1).

In order to reduce the pill burden the applicant is planning to market a new 300 mg strength capsule. The 200 mg and 100 mg capsules were used in Phase III and the applicant has performed a pivotal bioequivalence (BE) study using one 300 mg capsules (test) and a combination of one 100 mg capsule and one 200 mg capsule (reference).

The current review focuses on:

- Exploratory dose-response analyses for droxidopa for NOH symptom relief and blood pressure (BP), and
- Pivotal BE study for the 300 mg capsule strength

1.1 Summary of OCP Findings

The Office of Clinical Pharmacology (OCP) has reviewed the clinical pharmacology and biopharmaceutics (CPB) information provided in the NDA 203-202 and our observations are listed below:

- NOH is an orphan indication with limited treatment options and one might find some clinical utility in approving droxidopa for short term symptom relief. But the pattern of symptom relief based on CGI-S was comparable for both droxidopa and placebo groups

during the dose-titration phase. The observed intra-individual variability (~ 2.9 units) for OHSA Item-1 is much higher than the treatment effect of 1.0 unit favoring droxidopa and the treatment effect lost statistical significance after one week.

- The bioequivalence (BE) result from Study 104 is acceptable. However, the clinical and bioanalytical site inspection report from Office of Scientific Investigations (OSI) for this pivotal BE study is currently pending. The approvability of the 300 mg capsule strength depends on the findings from OSI.

1.2 Post Marketing Requirements/Commitments

The OCP review dated 01/25/2012 included a PMR for conducting a dedicated renal impairment study for droxidopa. The applicant had an active study protocol for this study at that time and was expected to submit the report post-approval during the first review cycle. However, the study was not completed after receiving complete response and the PMR from our prior review is still applicable.

Background of Efficacy Study 306

The initial objective of the phase III study 306 was to measure the durability of treatment effects with droxidopa. The change from baseline in orthostatic hypotension questionnaire (OHQ) composite score at week-8 was the original primary efficacy endpoint. However, after an interim analysis when about 60 % of enrolled patients either completed end of study visit or lost to follow-up, the applicant modified the study 306 by dividing it into two parts, 306A and 306B. Patients who were included in the interim analysis were grouped as study 306A and patients enrolled after the interim analysis and those patients who were not included in the interim analysis were considered as part of Study 306B. There were a total of 171 patients enrolled in study 306B, with 87 patients on droxidopa and 84 patients on placebo respectively. The original intent was to measure reduction in patient reported falls as the primary efficacy endpoint. But the statistical analysis plan (SAP) was changed prior to completion of 306B and the protocol amended to have change in Orthostatic Hypotension Symptom Assessment (OHSA) Item-1 (dizziness/light headedness) from baseline to week-1 after the dose titration phase (Visit 4, See Figure 1 below) as the primary efficacy endpoint. The study 306B is considered as the pivotal efficacy trial for this re-submission. Unlike the prior efficacy trials reported in the original submission (Studies 301 or 302), the study 306 included only Parkinson's patients with symptomatic neurogenic orthostatic hypotension (NOH).

2.1 Design of Study 306B

This was a multi-center, placebo-controlled, parallel-group, double-bind Phase III study in adult patients with symptomatic NOH associated with Parkinson's disease. The design features of Study 306B is shown in Figure 1. After screening for eligibility and at the end of the baseline visit (Visit 2) all eligible patients (~171) were randomized in a 1:1 ratio to treatment with either droxidopa or placebo. The patients then entered a double-blind dose-titration phase at 100 mg three times daily (TID) of droxidopa or matching placebo. Treatment was escalated in 100 mg TID increments until one of the following titration stopping criteria was met.

1. Patients becoming completely asymptomatic for NOH as reported on clinician recorded Clinical Global Impression score for severity (CGI-S). The CGI-S scores range from 1 to 7 and a score of 1 is considered normal or no NOH symptoms. The titration may also have been stopped when a patient became nearly asymptomatic (e.g. CGI-S score of 2, borderline NOH) in clinician's opinion, or

2. Patient's systolic blood pressure (BP) ≥ 180 mm Hg or diastolic BP ≥ 110 mm Hg after 10 minutes in supine position (with head and torso elevated at 30° from horizontal). The titration can also be stopped if the BP was close to the limits if necessary, or

3. Patient cannot tolerate the side effects with a dose, or

4. Patient reached the maximum allowed dose of 600 mg TID.

A patient can proceed directly to the 8-week double-blind maintenance phase at that dose after meeting criterion-1 at any stage of the dose titration. Patients who met criteria 2 or 3 can advance to the maintenance phase at the previous (one step lower) dose, except for those at the starting dose of 100 mg TID because they will be withdrawn from treatment. Patients who met criterion-4 can continue to the maintenance phase on 600 mg TID as their selected dose. The dose titration will be for up to 2-weeks depending on the number of titration steps involved (maximum 6 steps).

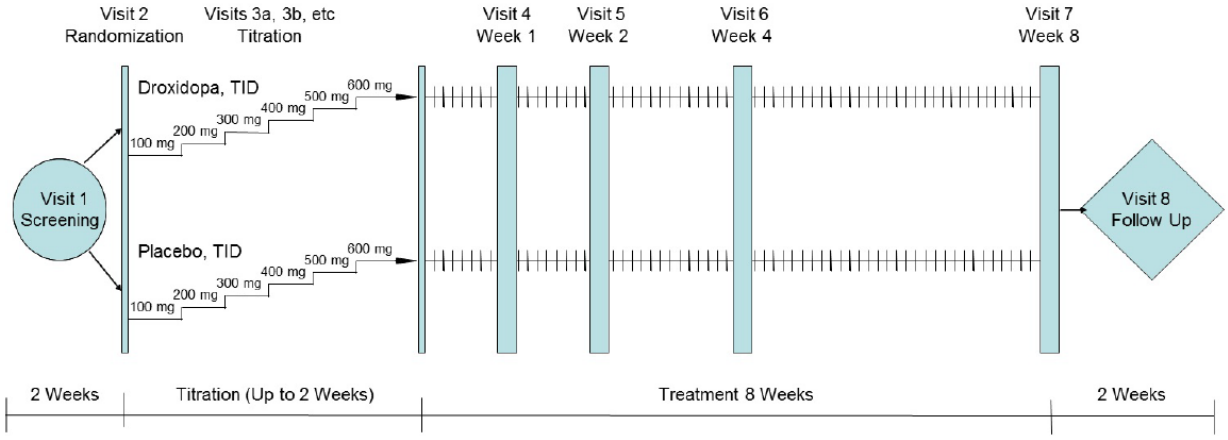


Figure 1. Design of study 306B in NOH patients with Parkinson's disease. There is a 2-week double-blind dose-titration phase, followed by 8-week double-blind maintenance phase. A total of 171 patients were enrolled in to this study (87 patients on droxidopa and 84 patients on placebo treatment groups respectively). The primary efficacy analysis was at week-1 (Visit 4) after the titration phase. *Ref: Figure 9-1 from Clinical Study Report, Page 22. \\cdsesub1\evsprod\NDA203202\0048\m5\53-clin-stud-rep\535-rep-effic-safety-stud\noh-symptoms\5351-stud-rep-contr\noh306b*

During the maintenance phase patients returned for study visits after 1, 2, 4 and 8 weeks of double-blind treatment (Visits 4, 5, 6 and 7 respectively). The CGI-S and orthostatic standing test (OST) for BP measurements were taken during each titration visits and maintenance visits. The OHQ composite, which includes OHSA and OHDAS scores, was done only at baseline and visits during the maintenance phase. Details of the patient reported outcome instruments used this study are described in detail previously (Ref. SEALD endpoint review by Dr. Elektra Papadopoulos DARRTS date 01/24/2012).

2.2 Efficacy Results

The primary efficacy endpoint for study 306B was mean change in OHSA Item-1 (dizziness/light headedness) from baseline to week-1 (visit 4) for the full analysis set (FAS). The FAS was mITT with all randomized patients who received at least one dose of study treatment and have reported OHSA Iten-1 at week-1. Of the 174 randomized patients, 171 patients received at least one dose of treatment (ITT) and 147 patients were included in FAS (N=78 on placebo and N=69 on droxidopa). Demographics and baseline NOH disease severity were similar between placebo and treatment groups. Study 306B showed a treatment effect of 1.0 (p=0.018) on OHSA Item-1 from baseline to week-1 favoring droxidopa (See Table 1 below). However, the observed intra-individual variability for OHSA Item-1 was 2.9 units on 11 point scale (Ref. Statistical Review by Dr. Jialu Zhang, DARRTS date 12/04/2013).

Table 1. Average OHSA Item-1 Scores from Study 306B

Visits/Treatment	Placebo	Droxidopa
Baseline (Randomization)	5.1 (2.3), N=78	5.1 (2.0), N=69
Week-1 (Visit-4)	3.8 (2.8), N=78	2.8 (2.4), N=69
Week-2 (Visit-5)	3.3 (2.3), N=75	3.3 (2.7), N=68
Week-4 (Visit-6)	3.6 (2.6), N=73	2.1 (2.6), N=67
Week -8 (Visit-7)	3.6 (2.6), N=68	3.0 (2.8), N=63

OHSA Item-1 values are Mean (SD), FAS for week-1. Primary efficacy analysis is at week 1 and excluded patients who discontinued prior to week-1.

The change from baseline on SBP during OST also favored droxidopa group at week-1 (an improvement of about 6.4 mm Hg on droxidopa versus 0.7 mm Hg on placebo for the lowest SBP recorded from +0 to +3 minutes on OST). There were more discontinuations prior to week-1 in the droxidopa group (N=18) compared with the placebo group (N=6) and were thought to be discontinuations related to adverse events. The secondary efficacy variables included mean change in OHSA Item-1 from baseline to weeks-2, 4 and 8. The observed difference from placebo were -0.2 (p=0.6), -0.5 (p=0.308) and -0.6 (p=0.187) at weeks-2, 4 and 8 respectively for droxidopa treatment.

2.3 Exploratory Dose-Response Analyses

Previous Phase III studies (301 and 302) had open label dose-titration with only droxidopa (and no placebo) and our analyses reported in the previous review may have been confounded by the placebo response over time. Also, the dose-escalation criteria in those trials were different (based on OHSA Item-1 and BP while 306B used CGI-S mainly). The double-blind, parallel group design of study 306B provided a direct comparison between droxidopa and placebo.

In study 306B, the distribution of doses on droxidopa and placebo groups were almost comparable (Figure 2) with about 40 % and 48 % of patients requiring the maximum dose of 600 mg TID for droxidopa and placebo respectively, while about 7-8 % of patients remained with the lowest dose of 100 mg TID on both treatment groups.

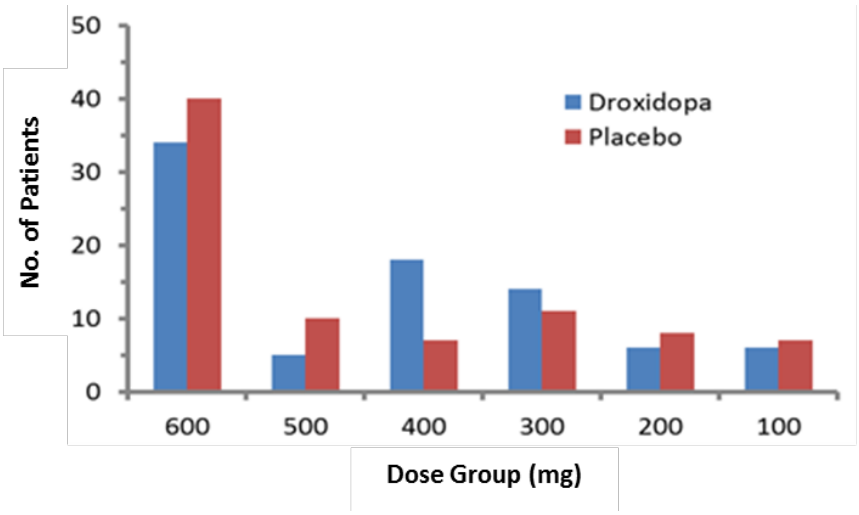


Figure 2. Distribution of doses in the droxidopa and placebo treatment groups. Assigned dose information from dataset ADCGI.xpt

The clinician reported CGI-S was used for dose escalation (not OHSA Item-1) and CGI-S was the only measure for symptom relief available during the titration phase. Lowest standing SBP from OST is a hemodynamic measure related to NOH condition and OSTs were performed after CGI-S assessments in each patient. Therefore, exploratory dose-response analyses were carried out for both droxidopa and placebo patients for CGI-S and lowest standing SBP from OST.

The symptom relief, as measured with clinician reported CGI-S showed a similar pattern for both droxidopa and placebo treatments during dose-titration. This was also evident from the comparable distribution of doses in the droxidopa and placebo groups. Since CGI-S was also reported during the maintenance visits it was possible to evaluate the durability of treatment effects on droxidopa and placebo (Figure 3A and 3B) and the treatment effects generally declined over time. This was in agreement with the observation that primary efficacy variable OHSA Item-1 also declined over time and lost statistical significance after week-1 (Visit-4).

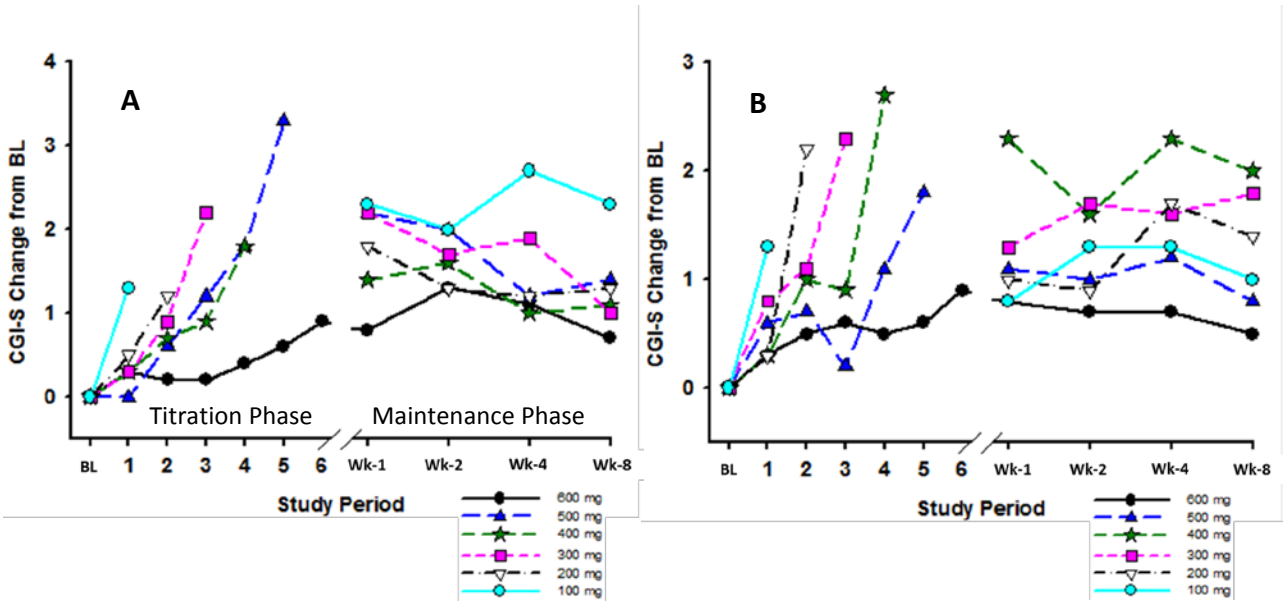


Figure 3. Mean improvement from baseline for clinician reported CGI-S scores during the double-blind dose-titration phase and 8-week maintenance phase with **droxidopa (A)** and **placebo (B)**. Each line represents a maintenance dose group as patients are dose-titrated, starting with 100 mg TID on the first day to a maximum dose of 600 mg TID. BL stands for baseline and there are 6 possible dose titration steps. For example, patients who had 600 mg TID as their individualized dose went through all 6 dose titration steps, 100, 200, 300, 400, and 500 mg TID before reaching their optimal dose of 600 mg TID, whereas patients who had 100 mg TID as their individualized dose did not have any other dose level. See dose titration criteria for details. The X-axis break denotes the transition from dose-titration phase to maintenance phase. Data source: ADCGI.xpt

As per the proposed mechanism of action of droxidopa (that it shows pharmacological effects by releasing norepinephrine) a dose dependent effect on BP was expected. But there were no clear dose dependent effects on SBP with droxidopa treatment (Figure 4A) probably because the dose-escalation was based on symptom relief (CGI-S) and not on BP. The placebo treatment did not show any dose dependent effects on SBP unlike the symptom relief seen on CGI-S (Figure 4B).

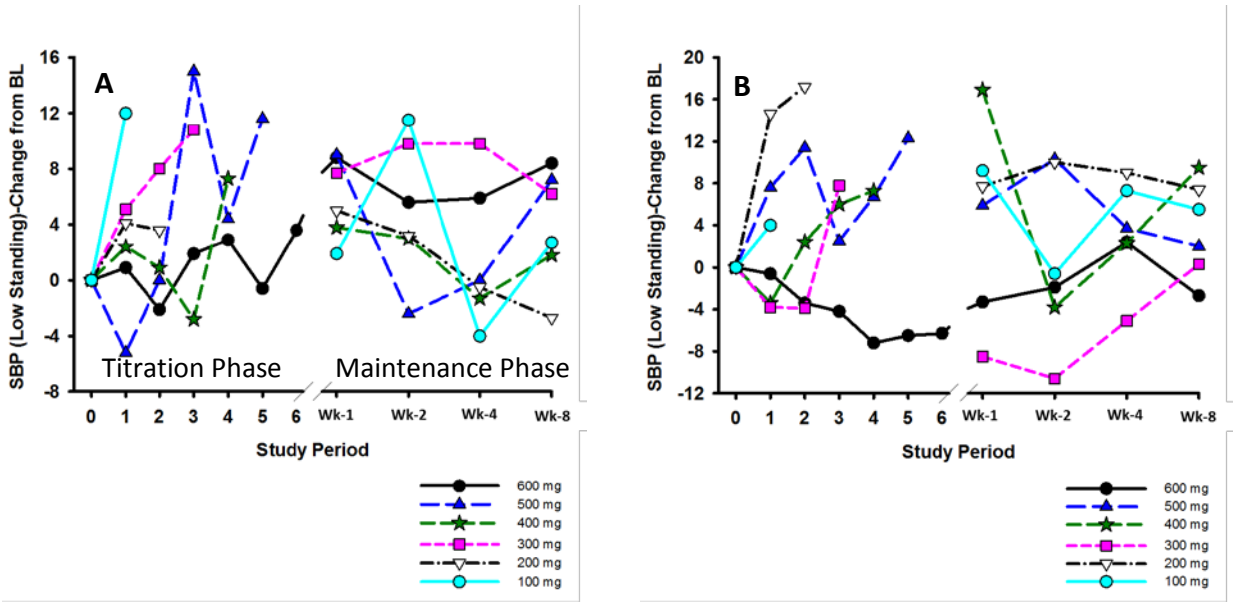


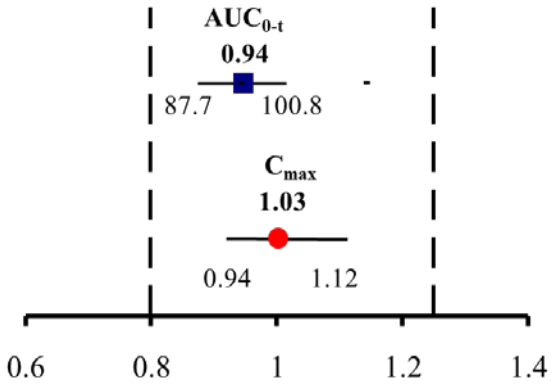
Figure 4. Mean change from baseline for lowest standing systolic BP (mm Hg) from OST during the double-blind dose-titration phase and 8-week maintenance phase with **droxidopa (A)** and **placebo (B)**. Each line represents a maintenance dose group as patients are dose-titrated, starting with 100 mg TID on the first day to a maximum dose of 600 mg TID. Data source: ADORTH.xpt

2.4 Observations from Study 306B

- Study 306B showed a statistically significant treatment effect of 1 unit difference on OHSA Item-1 (on a 11 point scale) favoring droxidopa over placebo
- Clinical significance of the observed treatment effect of 1 unit for OHSA Item-1 is not well understood. The observed intra-individual variability is ~ 2.9 units for OHSA Item-1.
- There was significant placebo response for NOH symptom relief as evident from clinician reported CGI-S scores during dose-titration.
- The observed, statistically significant treatment effect for OHSA Item-1with droxidopa was sustained only for a week during the maintenance phase. The treatment effect generally declined and lost statistical significance during the 8-week maintenance phase.

Pivotal BE Study

Study No. 104 Study Period: 2013	**Title:** A Randomized, Open-Label, Bioequivalence Study of one 100 mg and one 200 mg Capsule of Droxidopa versus one 300 mg Capsule of Droxidopa in Healthy Subjects
EDR Link:	\\cdsesub1\evsprod\NDA203202\0044\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\noh104
Primary Objective: To demonstrate bioequivalence (BE) of one 100 mg capsule and one 200 mg capsule of droxidopa versus one 300 mg capsule of droxidopa in healthy subjects	
Study Design: Open-label, randomized, 2-period, 2-treatment, single-dose, cross-over study Reference Treatment: One 100 mg, Lot # HSDC and one 200 mg capsule, Lot # HSDG (Treatment A) Test Treatment: One 300 mg capsule, Lot # KSPB (Treatment B) Note: Subjects fasted overnight, single dose test/reference treatment was administered with 240 ml water and the first meal was 4 hours after dosing. A 3-day wash-out period was used between treatments.	
Study Population: Healthy adult male/female subjects (N=24), 18-65 years of age with BMI 18-35 kg/cm^2. Women should not be nursing or pregnant.	
Analytical Method: Validated LC-MS/MS method for used for quantifying droxidopa from blood plasma. Calibration range 5-3000 ng/ml.	
PK Sampling: Pre-dose, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12 and 24 h post dose	
Statistical Method: ANOVA on log transformed parameters fitting for sequence, period, and treatment. LS mean and 90 % CI for the difference were constructed.	
Results: The figure below shows the ratio of LS means of test divided by reference treatments for primary PK parameters and their 90 % confidence intervals (N=24). Dotted vertical lines shows the BE lower and upper limits of 0.8 and 1.25 respectively.	



The observed median t_{max} for droxidopa was 3 hours for both test and reference treatments. There were no deaths, serious adverse events or discontinuations due to an adverse event in this study.

Site Inspection: A clinical and bioanalytical site inspection is being conducted by OSI and the inspection report is currently pending.

Reviewer's Comments:

- *The 300 mg capsule is bioequivalent to a combination of one 100 mg capsule and one 200 mg capsule. However, the approvability of the 300 mg strength depends on the OSI inspection report.*

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/s/

SREEDHARAN N SABARINATH
12/05/2013

YANING WANG
12/05/2013

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